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Acta Obstetricia et Gynecologica Scandinavica publishes original papers and articles on clinical and experimental research work done in the Scandinavian countries in the fields of obstetrics and gynecology It brings you the best up to date information on developments and recent progress in these medical fields in the Northern countries

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Contents

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SERUM LIPIDS AND FATTY ACID COMPOSITION OF SERUM LECITHIN IN THE NON PREGNANT STATE IN PATIENTS WITH PREVIOUS CHOLESTASIS OF PREGNANCY

Goran Samsioe

From the Department of Obstetrics and Gynecology (Head Prof S Brody) Sahlgren s Hospital University of Goteborg Goteborg Sweden

Abstract Serum lipids and fatty acid composition of serum lecithin were studied 8–21 months after delivery in 20 non pregnant women who during their latest pregnancy had presented signs of CP These women were compared with normal non pregnant women ($n=18$) and with patients with cholestasis of pregnancy (CP) ($n=$ 8) In the non pregnant state women with previous cholestasis of pregnancy (CP) showed in serum lecithin a low relative content of palmitic (16 0) and linoleic (18 2) acids and a high portion of stearic acid (18 0) These findings indicate as a basic defect in CP a reduction in liver lecithin synthesis via pathway I (Kennedy's pathway) in favour of an increased pathway II (Greenberg s pathway) These data further support the hypothesis of increased estrogen activity as an etiological factor in CP The basic influence by pregnancy on serum lipids and serum lecithin fatty acid composition was the same in women with CP as in women with a normal pregnancy

Cholestasis of pregnancy (CP) occurring in certain predisposed women is considered to be hormonally induced Among the gestational hormones estrogen has been suggested to be responsible by provoking impaired hepatic excretory function (2) An exaggerated reaction to normal amounts rather than abnormally high serum levels of estrogen to be a likely mechanism (25)

Serum lecithin relative fatty acid composition in CP is characterized as compared with normal pregnancy by a low palmitic acid (16 0) and a high oleic acid (18 1) content (11 13)

The influence of normal pregnancy on serum lecithin relative (and absolute) fatty acid composition are characteristic increases in palmitic (16 0) and oleic (18 1) acids and decreases in stearic (18 0) linoleic (18 2) and arachidonic (20 4) acids (22)

4–762861

The present paper deals with serum lipids and fatty acid composition of serum lecithin as determined by gas liquid chromatography (GLC) in non pregnant women with previous cholestasis of pregnancy studied 8–21 months after termination of their cholestatic pregnancy

MATERIALS AND METHODS

Clinical series

Twenty eight women with cholestasis of pregnancy pregnant CP (mean gestational week 34 9 range 6–40 weeks) were studied All patients presented a history typical for cholestasis of pregnancy and had immunologically detectable amounts of LP X in serum Apart from the cholestatic syndrome all pregnancies were uncomplicated at the time of blood sampling

According to an earlier definition (14 15) fourteen women were designated as pruritus gravidarum (PG) i e serum total bilirubin (1 2 mg/100 ml) and SGOT/SGPT (50 units/l) and fourteen as hepatosis of pregnancy (HP) i e total serum bilirubin above 1 2 mg/100 ml and/or SGOT and/or SGPT (50 units/l)

Twenty women with previously diagnosed cholestasis of pregnancy previous CP (mean age 7 0 years range 21–35 years) were re-examined 8–21 months after parturition All patients were healthy and had regular menstruations and no women were nursing their babies at the time of the study Pruritus had disappeared immediately after delivery and serum bilirubin and alkaline phosphatase values were normal During their cholestatic pregnancy 9 women were designated as pruritus gravidarum (PG) and 11 as hepatosis of pregnancy (HP) No patients were using oral contraceptives

Eighteen normal non pregnant healthy young women (mean age 6 2 range 19–34 years) with regular menstruation not using oral contraceptives served as a control series Blood samples were drawn on the first or second day of the menstrual bleeding

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2 Fjallbrant, B.. Immunoagglutination of sperm in cases of sterility Acta Obstet Gynec Scand *44* 47(1965
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4 Snyder F F & Hoskins F M.. *In* A Textbook of Obstetrics (ed D E. Reid) p 81 Saunders Philadelphia and London 1962.

When several papers by the same author are quoted, the papers should be numbered in chronological order

Text references should be indicated by figures within parentheses Examples the incidence is similar to that in other reports (1 5 11 17) Davies et al (6) have reported

General

Authors are requested in the interest of all concerned to restrict the length of papers as much as possible. Papers should not exceed 16 printed pages including tables and illustrations Exceptionally 24 pages can be allowed by the chief editor If a paper exceeds 12 printed pages (about 30 typewritten sheets) the cost for the excess pages as well as costs for tables and illustrations exceeding Sw Kr 300 will be borne by the author

Illustrations may be printed in colour if so requested but at the author s expense

Manuscripts exceeding 24 printed pages can be published as a supplement at the author s expense

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Proofs and reprints

The printer's proof (together with an order form) be sent to the principal author by the Editorial L It should be returned to the secretary without de Reprints of published articles should be ordered simultaneously

Table III *Mean differences (Δ) (mole per cent) in composition of major fatty acids of lecithin in women with previous pruritus gravidarum (PG) (n=9 mean age 24 range 20–30 years) previous hepatosis of pregnancy (HP) (n=11 mean age 28 range 20–34) versus normal non pregnant women (n=18 mean age 26 2 range 19–34)*

=0 05 level =0 01 level =0 001 level

	Non pregnant state Previous PG vs normal		Non pregnant state Previous HP vs normal	
	PC PC Δ	*P*	PC PC Δ	*P*
16 0	−1 5		−1 4	
16 1 (*n* 7)	+0 1	–	+0 1	–
18 0	+0 3	–	+1 1	
18 1 (*n* 9)	0 0	–	+0 1	–
18 2 (*n*-6)	−1 1	–	−2 9	
0 3 (*n* 6)	+0 6	–	+0 2	–
20 4 (*n* 6)	+0 7	–	+0 6	–
22 6 (*n* 3)	+0 1	–	+1 2	
18–22 (*n* 6)	+1 8		−0 4	–
18 2/20 4	−0 6	–	−0 7	–

14 0 15 0 18 3 (*n* 6) 18 3 (*n* 3) +.0 1 (*n* 9) 2 4 (*n* 6) 22 5 (*n*-6) and 22 5 (*n* 3) have been identified but not tabulated as their concentrations generally were less than 1% The fatty acid composition of phosphoglycerides was analysed but ony the results obtained in lecithin (PC) are tabulated as the fatty acid composition of lecithin more readily explains the metabolic influences (22)

Statistical methods

Conventional methods were used for the calculation of means standard deviations and standard error of means Student s *t* test was used to evaluate differences between groups Values of $p \leq 0\ 05$ were considered to be statistically significant

RESULTS

A Non pregnant state Previous CP compared with controls

In *serum lipids* (Table I) no differences were found in women with previous CP on comparison with the control series of non pregnant women

In the relative fatty acid composition of serum lecithin (PC) (Table II) in previous CP 16 0 (palmitic acid) ($p<0\ 01$) and 18 2 (linoleic acid) ($p<0\ 05$) were lower and 18 0 (stearic acid) higher ($p<0\ 05$) than in the controls

Yet in the subgroup of previous PG (Table III) 16 0 was lower ($p<0\ 05$) than in the controls In the subgroup of previous HP (Table III) all characteristic changes of previous CP were present i e 16 0 ($p<0\ 01$) and 18 2 ($p<0\ 05$) were lower and 18 0 higher ($p<0\ 05$)

As the absolute amounts of lecithin (Table IV) were not different (191 and 198 mg/100 ml respectively) in the two groups these differences between previous CP and controls still persist when cal

Table IV *Composition of major fatty acids and mean differences (Δ) in women with cholestasis of pregnancy (n=28 week of gestation mean 34 9 range 26–40) and in non pregnant women with previous cholestasis of pregnancy (n=20)*

Figures are given in mole per cent of methyl esters
=0 05 level =0 01 level =0 001 level

	Cholestasis of pregnancy					
	Pregnant		Non pregnant		Pregnant vs non pregnant	
	X	S E M	X	S E M	PC PC Δ	*P*
16 0	34 7	0 43	28 3	0 29	+ 6 4	
16 1 (*n* 7)	1 3	0 07	0 8	0 04	+ 0 5	
18 0	10 1	0 29	14 6	0 24	− 4 5	
18 1 (*n* 9)	14 4	0 41	11 8	0 30	+ 2 6	
18 2 (*n*-6)	24 3	0 69	24 6	0 62	− 2 1	
0·3 (*n* 6)	3 2	0 11	2 5	0 18	+ 0 7	
0 4 (*n* 6)	6 1	0 24	7 6	0 76	− 1 5	
22 6 (*n* 3)	3 9	0 23	4 5	0 34	− 0 6	
18–22 (*n*-6)	33 9	0 53	36 8	0 48	− 2 9	
18 2/20 4	4 4	0 30	3 6	0 19	+ 0 8	
Fatty acid mg/100 ml	117	5 7	86	4 9	+31	

Table V *Composition of selected fatty acids and mean differences (Δ) in lecithin and calculated lecithin in women with cholestasis of pregnancy (n=28 week of gestation mean 34 9 range 26–) and in non pregnant women with previous cholestasis of pregnancy (n=20)*

Fatty acid in lecithin	Pregnancy Lecithin (mg/100 ml)	Non pregnant Lecithin (mg/100 ml)	Δ	Pregnancy vs non pregnant *P*
16 0	86 6	50 0	+36 6	0 001
18 0	27 8	28 5	− 0 7	N S
18 1 (*n* 9)	39 2	22 7	+16 5	0 001
18 2 (*n* 6)	66 0	50 9	+15 1	0 001
20 4 (*n* 6)	17 8	15 8	+ 2 0	0 001
18–22 (*n* 6)	95 2	73 2	+22 0	0 001
Lecithin mg/100 ml	269	191	78	0 001

culated on absolute amounts of lecithin i e lecithin mg/100 ml with one particular fatty acid

B *Previous CP compared with CP*

All *serum lipids* (Table I) were lower in the non pregnant state (in women with CP) than during pregnancy (CP) Serum cholesterol was reduced after pregnancy by 77 mg/100 ml ($p<0\ 001$) serum triglycerides by 162 mg/100 ml ($p<0\ 001$) and calculated lecithin by 78 mg/100 ml ($p<0\ 001$)

In the *relative fatty acid composition* of serum lecithin (PC) (Table IV) in the non pregnant state (previous CP) 16 0 (palmitic acid) ($p<0\ 001$) and 18 1 (oleic acid) ($p<0\ 001$) were lower and 18 0 (stearic acid) ($p<0\ 001$) 18 2 (linoleic acid) ($p<0\ 001$) 20 4 (arachidonic acid) ($p<0\ 001$) and sum (*n* 6) ($p<0\ 001$) higher than in the pregnant state (CP)

Calculated as absolute amounts (Table V) i e lecithin in mg/100 ml with each particular fatty acid in previous CP 16 0 18 1 18 2 20 4 and sum of (*n* 6) all were lower ($p<0\ 001$) than in CP

DISCUSSION

Women with previous CP (studied 8–21 months after delivery) showed serum lipid values in agreement with those of healthy non pregnant women of the same age The marked increase in serum lipids characteristically seen in CP was not found after delivery in the previous CP group

Women with previous CP showed a low relative content in serum lecithin of palmitic (16 0) and linoleic (18 2) acid and a high proportion of stearic acid (18 0) as compared with the non pregnant controls The characteristic reduction in palmitic acid was also present in the subgroups designated as previous PG and previous HP

The same influences by pregnancy as seen in normal women (22) on serum lecithin relative fatty acid composition were experienced when patients with CP were compared with women with a previous CP i e high content of palmitic (16 0) and oleic acids (18 1) and low portion stearic (18 0) linoleic (18 2) and arachidonic (20 4) acids

In this comparison it should be pointed out that pregnancy in CP prone women causes a less marked increase in palmitic acid and a more pronounced increase in oleic acid concomitant with a lesser decrease in stearic and linoleic acids

An increase in serum lecithin during pregnancy is most likely due to increased synthesis in the liver (1) In the liver lecithin is synthesised along different intra cellular pathways The major pathways are *pathway I* cytidine diphosphate (CDP) choline diglyceride pathway (Kennedy pathway) and *pathway II* cytidine-diphosphate (CDP) ethanolamine methylation pathway (Greenberg's pathway) Pathway I is the faster and quantitatively most important (16 20) This pathway preferably gives in 1 position palmitic acid (16 0) and in 2 position linoleic (18 2) or oleic acid (18 1) (. Pathway I in the liver is stimulated *in vivo* (in the rat) (3) and *in vitro* (human liver slices) (6) by the presence of bile acids

Pathway II is the important source of lecithin containing in 1 position stearic acid (18 0) and in 2 position arachidonic acid (20 4) as well as other poly unsaturated fatty acids of longer chain length and greater unsaturation (e g 22 6) (21) In the

animal *in vivo* and *in vitro* studies indicate that pathway II is more active in the female (17 26) as well as during estrogen administration (18) Studies during the menstrual cycle in young women suggest that this influence by estrogens on pathway II is applicable also in man (10)

In a previous study (12) it has been shown that pregnant women in the early stage of CP hepatosis of pregnancy (HP) of short duration (before a major influence of raised bile acids on liver lecithin synthesis) have a characteristically high relative content of stearic acid (18 0) and arachidonic acid (20 4) in serum lecithin These findings were interpreted as an indicator of an enhancement of liver lecithin synthesis through pathway II due to an increased influence of estrogens

In the present study in non pregnant women with previous CP a high relative content of stearic (18 0) and arachidonic (20 4) acids in serum lecithin suggests that already in the non pregnant state of patients with previous CP (without pruritus and with normal liver function tests) an enhanced lecithin synthesis by pathway II is at hand Simultaneously occurring low palmitic (16 0) and linoleic (18 2) acids suggest in addition a decreased activity of the liver lecithin synthesis through pathway I

These differences in relative fatty acid composition were still present when calculated on an absolute basis i e on lecithin (mg/100 ml) with each particularly fatty acid

A high frequency of gallbladder disease (as verified by X ray after pregnancy) in women with CP has been reported earlier (23) Gallstone formation is dependent on bile composition and lecithins have quantitatively and qualitatively been shown to be of importance in the solubility of cholesterol in bile In women with a history of CP an altered liver lecithin metabolism might therefore be responsible for the formation of lithogenic bile

The etiology of CP is unknown An increased liver sensitivity to estrogen has been suggested to be an important contributory factor The data presented suggest a basic defect present already in the non pregnant state of CP prone women reflected in liver lecithin metabolism i e an increased pathway II and a decreased pathway activity In vitro and in vivo studies in the animal as well as preliminary data in man suggest that estrogen is one factor that enhances liver lecithin synthesis through pathway II concomitant with a reduction of pathway I

ACKNOWLEDGEMENTS

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UROGRAPHY AND RENOGRAPHY IN THE FOLLOW UP OF PATIENTS WITH TOXEMIA OF LATE PREGNANCY

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Abstract We have studied 129 patients with toxemia of pregnancy two months post partum by urography and renography The same investigations were performed on 17 healthy parturients post partum 49 patients (38 8%) had an abnormality either in urography or renography 20 patients (15 5%) had an abnormal urogram and 42 (32 6%) an abnormal renogram The findings correlated so that 7 patients had an abnormal urogram with a normal renogram and 13 patients had an abnormality in both investigations 29 patients had only an abnormal renogram In the control series 3 patients had an abnormal urogram and the same patients also had an abnormal renogram We divided the studied patients into groups according to the clinical severity of toxemia Urographic and renographic findings were divided evenly in the series so that abnormalities were no more common in the severe cases Renography cannot be considered merely as a screening method when compared with urography in the follow up of toxemic patients but these investigations are complementary

If a patient with toxemia of pregnancy gives no history of previous hypertension or renal disease or if these conditions have not been observed during the first months of pregnancy it is difficult to decide what sort of toxemia is present The signs of toxemia during the first 24 weeks of pregnancy indicated a so-called superimposed toxemia Superimposed toxemia can also be suspected in cases when the secretion of urine and electrolytes is increased during the night compared with daytime (10) Only a careful re examination a few months post partum can ascertain the diagnosis In addition to the routine investigations such as recording the blood pressure and performing urine and blood tests some special investigations such as renal clearance tests isotope renography and intravenous urography are of value (3 5 7) Renal biopsy and renal angiography are available but are somewhat more complicated Using these investigations it has been shown that severe toxemia may be associated with pre-existing renal or cardiovascular disorders in more than half of the cases (6 7) These investigations suggest that the more carefully patients are examined the less so-called pure or classic toxemia can be observed Besides its theoretical significance this matter is also of great practical importance because classic toxemia usually will be cured without leaving any signs (4) while hypertension and renal disease may become aggravated by toxemia of late pregnancy and perhaps finally lead to uremia and untimely death

The purpose of this study is to investigate the occurrence of a possible renal abnormality in patients with toxemia by urography and renography As well known renography is a relatively easily performed investigation which upsets the patient only slightly Both renography and urography can be done on out patients Further the purpose of this study is to illustrate the correlation between these investigations and especially the use of renography as a possible screening method in the follow up of toxemia patients

MATERIAL AND METHODS

The survey was carried out at Kuopio Central Hospital on patients who delivered between 1 11 1968–31 12 1971 The total number of deliveries during this period was 5 76 toxemia (according to the American Committee on Maternal Welfare) occurred in 576 cases (10%) and the number of patients examined was 129 or 26% of the toxemia patients These patients were divided before renography and urography into groups laid down by the American Committee on Maternal Welfare as modified by Werkö in 1948 (11) as presented in Table I

To be able to compare the occurrence of a possible renographic or urographic abnormality with the severity of the toxemia we placed the patients in each grou

Table I *Division of the patients into groups laid down by the American Committee on Maternal Welfare as modified by Werko in 1948*

Clinical diagnosis	No of patients
I Mild pre-eclampsia	89
II Severe pre-eclampsia	29
III Eclampsia	1
IV Essential hypertension complicated by toxaemia of late pregnancy	10
V Renal disease complicated by toxaemia of late pregnancy	3
Total	129

order according to the clinical severity of toxemia Our scoring system is designed only for putting these patients in such an order

The criteria for severity were onset of toxemia signs duration of gestation at admission to hospital duration of stay in hospital duration of proteinuria maximum protein excretion average protein excretion systolic blood pressure when discharged average systolic blood pressure average diastolic blood pressure fetal weight age of fetus and Apgar score These criteria used for defining the severity of toxemia are presented in Table II

Average value maximum minimum and standard deviation of those criteria are also shown in Table II

For each criterion the patients got points minimum 1 point and maximum 129 points (129 patients) The most severe case in each category got 1 point and the mildest se got 129 points Thus the added points from all the 13 na determined the final order of the patients Many of atients got same total of points so there were 96 rent scores and the mildest case(s) was (were) there re the score of 96 in Fig 1

The patients were studied two months post partum by renography and urography

The investigation methods for renography were as follows (*a*) The labelled compound used was 20 μCi ¹³¹I hippuran diluted with sterile isotonic saline solution to 0 5–1 ml (*b*) The radiation detectors 1 75 × 2 NaI (Tl) were collimated so that the diameter of measuring area on skin was 10 cm and the distance of detectors from skin 19 cm (*c*) Measuring technique The measuring range 10³ imp/sec time standard 3 sec and the curve was recorded at a speed of 4 mm

The investigation method in urography As a contrast medium 20 ml Urografin® 60% (Schering) i v A control radiograph from abdomen was taken before administration of contrast medium The first exposure was made 1 min after injection and after this a compress was placed on lower abdomen The following radiographs 10 and 15 minutes after the injection and after removing the compress a final radiograph from the abdomen

The control series consisted of 17 patients who all had delivered in 1972 No signs of toxemia were observed in these patients and the deliveries were normal They were also studied at their postnatal examination and both renography and urography were performed two months post partum

RESULTS

Renographic findings are represented in Table III In this study a total of 42 cases (32 6%) had obvious evidence of abnormal tubular function The findings were either one sided or bilateral and appeared either as a retardation of the secretory phase or as a prolonged renal transit time Related to these there was possibly a spastic excretory phase or the excretion was gradual This sort of excretory phase was considered to give certain evidence of a functional condition and not of a lesion of tubular func

Table II *Criteria used for defining the severity of toxemia and average maximum minimum and standard deviation of the criteria in the patients studied*

No	Criteria	No of patients	Average value	Maximum	Minimum	S D
1	Onset of toxemic signs (weeks)	129	29 6	4[illegible] 0	13 0	7 3
2	Duration of gestation at admission (weeks)	129	35 3	43 0	16 0	5 1
3	Stay in hospital (days)	129	26 5	104 0	9 0	15 7
4	Proteinuria (days)	129	20 5	58 0	3 0	11 8
5	Maximum protein excretion (g/24 h)	129	[illegible] 4	15 4	0 0	[illegible] 6
6	Average protein excretion (g/24 h)	129	1 2	43 0	0 0	3 8
7	Systolic blood pressure at admission (mmHg)	129	151 9	2[illegible]0 0	110 0	2[illegible] 9
8	Systolic blood pressure when discharged (mmHg)	129	1[illegible]7 5	180 0	100 0	14 3
9	Average systolic blood pressure (mmHg)	129	136 7	174 0	101 0	12 7
10	Average diastolic blood pressure (mmHg)	129	89 4	108 0	57 0	9 4
11	Fetal weight (kg)	129	2 7	5 4	0 6	0 9
12	Age of fetus (weeks)	129	38 0	43 0	29 0	3 0
13	Apgar points	129	7 0	10 0	0 0	3 1

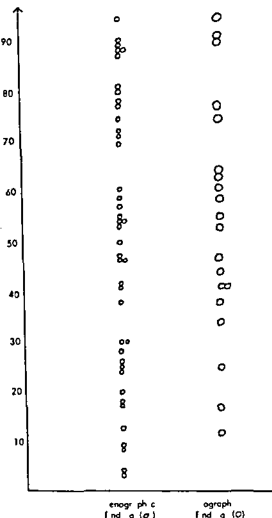


Fig 1 Abnormal renographic and urographic findings in patients divided into groups according to the clinical severity of toxemia (most serious case=1 mildest case=96)

ion There was one case with no secretion on one side and one case of hydronephrosis

Urographic findings are presented in Table IV 20 patients had abnormal urographic findings (15 5%) There were 7 patients with movable kidney 7 patients with morphological anomaly 1 patient with evidence of early hydronephrosis 1 patient with evidence of hydronephrosis and 2 of chronic pyelonephritis One patient with silent nephrosclerotic kidney One patient had a kidney with poor secretion which was evidence of nephropathy caused by diabetes the primary disease in this patient

Correlation between renography and urography In the series of 129 patients 42 patients had abnormal renographic findings and 20 patients abnormal findings on urography Of these patients 7 had an abnormal urogram with a normal renogram and 13 patients had abnormalities in both investigations 29 patients had only an abnormal renogram The relation between these findings is presented graphically in Fig 1

Fig 2 shows the division of the findings in regard to the previously defined severity of toxemia It can be observed that both abnormal urographic and abnormal renographic findings were divided quite evenly throughout the series

In the control series of 17 patients 3 patients had an abnormal renogram which in all of them appeared as a pathological secretory phase indicating an obvious lesion of tubular function All these patients had also an abnormal urogram 2 had a movable kidney and the third a moderate morphological anomaly

DISCUSSION

In the series of 129 patients 42 patients had an abnormal renogram (32 6%) and 20 patients (15 5%) had an abnormal in urogram 49 patients had abnormalities in either urography or renography (or in both) It was earlier known that 3 patients had renal primary disease and in addition 10 patients had essential hypertension 116 patients were considered to have a pure toxemia either a

Table III *Abnormal renographic findings 2 months post partum in the toxemia patients studied*

Abnormal renographic finding	Mild pre eclampsia	Severe pre eclampsia	Eclampsia	Essential hyper tension complicated by toxemia of late pregnancy	Renal disease complicated by toxemia of late pregnancy
Pathological secretory phase (40)	27	9	1	1	-
Silent kidney (1)					1
Hydronephrosis (1)		1			
Total renographic changes (42)	27/86	10/29	1/1	1/3	3/10

Table IV *Abnormal urographic findings 2 months post partum in the toxemia patients studied*

Abnormal urographic finding	Mild pre eclampsia	Severe pre eclampsia	Eclampsia	Essential hyper tension compli cated by toxemia of late pregnancy	Renal disease complicated toxemia of la pregnancy
Movable kidney (7)	3	3			1
Morphological anomaly (7)	5	1			1
Chronic pyelonephritis (2)	2				
Pre hydronephrosis (1)	1				
Hydronephrosis (1)					1
Poorly functioning kidney (1)				1	
Silent nephrosclerotic kidney (1)	1				
Total urographic changes (20)	12/86	4/29	0/1	1/3	3/10

mild pre-eclampsia severe pre eclampsia or eclampsia

In a previous study of 44 patients with toxemia Koskela and Pystynen (7) found a renal abnormality on urography in 14 patients (32%) Bedford et al (2) studied a series of 100 patients with toxemia by post partum urography and they observed an abnormality in 38 patients (38%) Compared with our study they had significantly more abnormal findings as result of urographic investigations In our series an abnormal urogram was observed in 20 patients (15 5%) 14 of these cases did not require repe ed examinations (movable kidney morpholog anomaly) by 6 patients repeated examinations w necessary

Laakso has studied patients with toxemia by nography (8) The most important object of study was the observation and follow up of tubu lesions in toxemia patients Before delivery the cretions is retarded and after delivery when condition of the patient improves the secreti usually also improves In normal parturients sec tion does not change during the pregnancy Niei nen et al (9) observed that also in the second a third trimester of normal pregnancy both excreti and secretion can be retarded

Bockler et al (3) found that 28 out of 77 patie with toxemia examined a few days after delive had an abnormal renogram In a re examinati 7–14 months post partum only 6 patients had pathological renogram In our study there was a a significant number 32 6% of pathological nographic findings when examined 2 months p partum Obviously findings of this sort are to a gr extent reversible as Bockler et al has obser (3) and therefore their actual significance is diffic to evaluate

In our study both the abnormal renographic a urographic findings are divided evenly in the wh series and e g no accumulation of patholog findings in patients with severe toxemia w observed as shown in Fig 2

Earlier Aantaa et al (1) have compared the r tion between abnormal renographic and urogra findings in gynecological patients Our study these patients with toxemia lead to similar con sions The correlation between renograph a

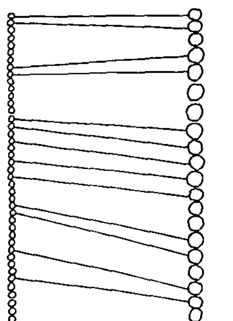


Fig 2 Correlation of abnormal urographic and renographic findings Abnormalities in the same patient are connected with a line

urographic findings which has been earlier discussed shows that renography cannot be considered merely as a screening method when compared with urography but these investigations are complementary renography reveals disturbances in renal (tubular) function and urography shows the more severe morphological abnormalities and changes

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DECREASE IN THE MORTALITY RATES FOR LOW BIRTH WEIGHT INFANTS AFTER PHENOBARBITONE TREATMENT

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bstract A daily dosage of 100 mg phenobarbitone dministered orally to pregnant women for three days or ore immediately before delivery has reduced the various ortality rates for low birth-weight infants by 50% or ore Since it is hardly possible to treat all pregnant omen in this way it is recommended to administer henobarbitone to women with high risk pregnancies such s former stillborn infant former premature delivery regnancy complications and planned induction of pre ature labour before the 37th week and until delivery kes place If the mothers of low birth weight infants ave not been adequately treated it is recommended that e newborn infant be given phenobarbitone injections mmediately after birth and at 8-hour intervals 10 injec ons in all

1968 I published a preliminary communication 7) about a possible drop in the first week ortality rate for low birth weight infants after enobarbitone treatment The series was small d the difference was not statistically significant the meantime the series has been increased and w comprises 805 single born infants The results e encouraging

MATERIAL AND TREATMENT

en we exclude all infants with lethal malformations and rhesus affected infants 911 single-born infants weighing 50–<–500 g were delivered in the obstetrical depart nt during the period January 1 1968 to December 31 71 All the mothers had been booked and controlled in ante natal clinic More than one third (i e 3 0) of the pregnant women received phenobarbitone viz 51 h pre-eclamptic toxaemia (according to our usual ctice) and 59 chosen at random The drug was given lly the dosage was 50–200 mg per day and was con ed until delivery took place In addition 10 epileptic received phenobarbitone all through the preg

All the live-born infants except some in good health from the highest weight-class were transferred to the Department of Neonatology where every second infant was treated with phenobarbitone intramuscularly in the following way The initial injection after birth and the following nine injections at 8 hour intervals Each dose was 1 mg to infants of 1000 g or less 2 mg to infants of >1000 to ≤1500 g 3 mg to infants of >1500 to ≤2000 g and 4 mg to infants of >2000 to ≤2500 g It had been planned in advance that the initial injection should be given immediately after birth but in practice it was unfortunately not given until 5–15 minutes after and sometimes even 2 hours later In some cases the midwives forgot to give the infants the initial injection and in consequence they were not treated at all

106 infants (4 stillborn and 10 live born) born to mothers treated for less than 3 days (most often less than 4 hours) were excluded because we have found that it takes a couple of days before the phenobarbitone concentration in serum from a pregnant woman reaches 1 μg per ml and about a week before a fixed daily dose of phenobarbitone reaches a stable serum-phenobarbitone level A daily dose of 50 mg or 100 mg of phenobarbitone results in a stable concentration of 3–6 μg per ml and 6–1 μg per ml respectively (investigations together with Johs Christiansen unpublished) In an earlier publication (24) it was shown that the phenobarbitone concentration in umbilical-cord serum is 95% of the mother s serum value

The reduced series comprises 805 infants i e 6? still born and 743 live born

Autopsy on all the stillborn and neonatally dead infants was performed by the Laboratory of Paediatric Pathology

The reduced series was divided into two groups (Table I) (A) No administration of phenobarbitone to the pregnant woman and (B) Administration of phenobarbitone to the pregnant woman for three days or more immediately before delivery In both groups it has been disregarded whether or not the infant had been given phenobarbitone

The two groups differ only with regard to the number of women with pre-eclamptic toxaemia In group A there were only 2% and most often mild cases at that In group B there were 26% with many severe cases Being aware that the two groups are not comparable I examined the outcome when all infants of women with pre-eclamptic

24 hours in 23 of 40 i e 58% In group B none of the three dead infants died during the first 24 hours The striking difference may be accidental and due to the small numbers

All the dead infants had more or less pronounced atelectasis of the lungs The causes of death are discussed later

Respiratory distress syndrome (RDS) has been found in 70% of the first week deaths and in 14% of the live infants in group A In group B the figures are 33% and 14% respectively The incidence of RDS among all live born infants in group A is 17% and in group B 14% These figures show that phenobarbitone treatment of the woman does not have any influence on RDS

I have also examined the *first 4 weeks neonatal mortality rate* (first 28 days deaths per 1000 live births) in order to see if the good results for the early neonatal mortality rate was due to a postponement of the time of death (Table V) Statistically the good results were less pronounced but the trend was still the same The causes of death are discussed later

Finally the *late perinatal mortality rate* (stillbirths+first 28 days deaths per 1 000 stillbirths+live births) is shown in Table VI The results are encouraging as it appears from the statistical significance

The influence of phenobarbitone treatment on the infant In the above calculations it has been disregarded that alternate live born infants were treated with phenobarbitone If group A is subdivided into subgroups (I) nontreated infants and (II) infants treated with phenobarbitone a comparison of the various mortality rates (early neonatal first 4 weeks neonatal and late perinatal) between subgroups I and II shows that for all three rates subgroup II is lower (as shown in Fig 1 for the weight class ≥750 – <2 500 g) but the differences are not statistically significant The discrepancy between the numbers in the two subgroups i e 298 in subgroup I compared with 249 in subgroup II is due to the fact that in 24 cases the midwives forgot to give the initial injection of phenobarbitone and in consequence these infants were not treated at all They survived the first 4 weeks of life and were included in subgroup I

In group B the problem is more complicated First it must be examined how the variation in dosage and duration of phenobarbitone treatment to the mother influenced the number of the first 4 weeks neonatal deaths Table VII shows an even distribution of the neonatal deaths among the mothers who received 50 mg of phenobarbitone per day but not among the mothers who received 100 mg or more The mortality for infants of the former was 6 out of

Table III *Number of pregnant women dosage and duration of treatment*

Stillbirths in brackets

Days	Daily dose of phenobarbitone in mg			
	50	100	≥150	Total
< 7	16 (1)	11	8 (1)	35 (?)
<14	18	28 (2)	7 (1)	53 (3)
	26 (1)	62 (?)	28	116 (3)
Total	60 (?)	101 (4)	43 (?)	204 (8)

No demonstrable cause of stillbirth

Table IV *Early neonatal mortality rate per 1 000 live births*

Weight-classes (g)	Group A	Group B	Value of $P=2\alpha$	Reduction (%)
≥ 750–<1 000	818	–	NS	
≥ 750–<1 500	386	59	<0 0?	
≥ 750–<? 000	206	29	=0 004	
≥ 750–<2 500	73	15	=0 002	80
≥1 000–<1 500	305	67	NS	
≥1 000–<2 000	164	29	<0 005	
≥1 000–<? 500	58	16	<0 0?	72
≥1 500–<2 000	80	19	NS	
≥1 500–<2 500	27	11	NS	59
≥2 000–<2 500	13	8	NS	39

Table V *First 4 weeks neonatal mortality rate per 1 000 live births*

Weight-classes (g)	Group A	Group B	Values of $P=2\alpha$	Reduction (%)
≥ 750–<1 000	818	–	NS	
≥ 750–<1 500	414	?94	NS	
≥ 750–<2 000	2?9	100	<0 03	
≥ 750–<2 500	80	41	<0 08	49
≥1 000–<1 500	339	333	NS	
≥1 000–<2 000	189	103	NS	
≥1 000–<2 500	65	41	NS	37
≥1 500–<2 000	100	38	NS	
≥1 500–<2 500	31	17	NS	45
≥2 000–<? 500	13	8	NS	39

Table VI *Late perinatal mortality rate per 1000 stillbirths+live births*

Weight-classes (g)	Group A	Group B	Value of $P=2\alpha$	Reduction (%)
≥ 750–<1 000	905	333	NS	
≥ 750–<1 500	564	455	NS	
≥ 750–<2 000	376	171	<0 002	
≥ 750–<2 500	163	78	<0 003	52
≥1 000–<1 500	466	473	NS	
≥1 000–<2 000	318	164	<0 02	
≥1 000–<2 500	136	75	<0 03	45
≥1 500–<2 000	224	56	≈0 008	
≥1 500–<2 500	89	33	<0 02	63
≥2 000–<2 500	49	23	NS	53

58 (average weight 1971 g) and for infants of the latter 2 out of 138 (average weight 2025 g) The causes of death were as follows *Col 1A* 2 infants weight 1180 g and 1800 g both mothers had a severe pre-eclamptic toxaemia *Col 1B* 2 infants weight 1300 g and 2170 g the former died from a sepsis which developed neonatally the latter had a subtotal atelectasis of the lungs but no RDS otherwise there was not any demonstrable cause *Col 1C* 2 infants weight 1350 g and 1490 g both died because of a neonatally developed infection sepsis and pneumonia *Col 2B* The infant weighted 120[illegible] g the mother had a chronic hypertension and [illegible] severe abruptio placentae *Col 3C* The infan[illegible] weighed 1980 g died because of a neonatally an[illegible] en pneumonia The higher mortality among infan[illegible] to mothers who received only 50 mg daily is statis[illegible] cally significant ($P=2\alpha<0$ 02)

Six out of 8 dead infants in Table VII wer[illegible] treated with phenobarbitone The remaining 2 non treated infants were born to mothers who had re[illegible] ceived 50 mg daily

The table seems to imply two important facts Firstly that it is of no value to administer pheno[illegible] barbitone injections to the infant if the mothe[illegible] has been given 100 mg of phenobarbitone or mor[illegible] daily Secondly that the same good results cann[illegible] be reached by giving the mother 50 mg o[illegible] phenobarbitone daily even if the infant is give[illegible] phenobarbitone injections In other words it is th[illegible] infant s serum phenobarbitone concentration a[illegible] birth which plays a decisive part in obtaining th[illegible] good results

A comparison of the various mortality rates be[illegible] tween subgroup I subgroup II and group B under[illegible] taken in the same way as shown in Tables IV [illegible] shows that for each factor group B has the low[illegible] rates as demonstrated in Fig 1 for the weight-cla[illegible]

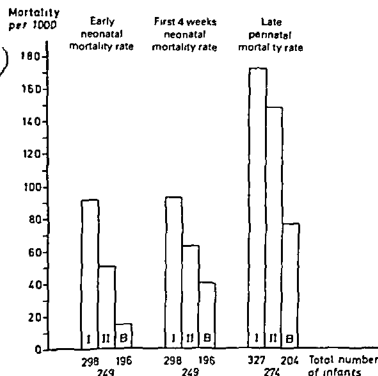


Fig 1 The various mortality rates fo[illegible] weight class ≥750 – <2500 g I [illegible] treated infants from group A II [illegible] nobarbitone treated infants from grou[illegible] B group B The difference betwe[illegible] and II is not statistically significant fo[illegible] of the three mortality rates The diff[illegible] between II and B is statistically sign[illegible] only for the late perinatal mortal[illegible] ($P=2\alpha<0$ 03) The difference betw[illegible] and B is statistically significant for all rates ($P=2\alpha<0$ 001 0 04 and 0 00[illegible])

Table VII *Number of pregnant women with live born infants Dosage and duration of treatment*

Every second live-born infant was treated with phenobarbitone The first 4 weeks neonatal deaths are shown in brackets

	Days	Daily dose of phenobarbitone in mg Col 1 50	Col 2 100	Col 3 ≥150	Total
A	≥3–< 7	15 (2)	11	7	33 ( )
B	≥7–<14	18 ( )	26 (1)	6	50 (3)
C	≥14	25 (?)	60	28 (1)	113 (3)
Total		58 (6)	97 (1)	41 (1)	196 (8)

1 One of these did not receive phenobarbitone treatment

≥750–<2 500 g Furthermore there is more often statistical significance between subgroup I and group B than was the case between group A and group B On the other hand the statistical significance is less frequent between subgroup II and group B than was the case between group A and group B

The causes of death for the infants who died during the first 4 weeks of life (Table VIII) In a number of cases there were pregnancy complications which contributed to the neonatal death In subgroup I this was the case with 4 of 28 (i e 14 3%) viz 1 with diabetes mellitus (White class D) 1 with placenta praevia and 2 with a mild abruptio placentae The infants born to the three last mentioned mothers had RDS In subgroup II there were 3 of 16 (i e 18 8%) viz 1 with diabetes mellitus (White class D) and 2 with placenta praevia These 3 infants had RDS In group B there were 3 out of 8 (i e 37 5%) viz 1 with chronic hypertension and a severe abruptio placentae and two with pre-eclamptic toxaemia very low values of estriol in urine and more than half of the placenta was degenerated (white infarcts) None of these children had RDS

In a number of other cases neonatal complications arose which in association with RDS caused the death Thus in 5 infants in subgroup I pneumonia pneumothorax and rupture of falx cerebri The autopsy also showed that 2 of the infants had kernicterus In subgroup II 5 infants had sepsis purulent meningitis pneumonia and rupture of the liver with haemoperitoneum In group B 4 infants had sepsis and pneumonia one of them had Down s syndrome as well

The remaining 28 cases all died within the first three days except one who died 108 hours old 18 of them had RDS The post mortem examination showed various degrees of atelectasis of the lungs and in many hyaline membranes The infants are distributed 19 in subgroup I 8 in subgroup II and 1 in group B (whose mother had received 50 mg of phenobarbitone for 8 days but who had not received phenobarbitone itself)

Table VIII gives a summary of the causes of death The big difference in the mortality between subgroup I subgroup II and group B at No demonstrable complications etc is immediately evident There is statistical significance between I and B ($P=2\alpha=0\ 001$) between I and II+B ($P=2\alpha<0\ 005$) and between I+II and B ($P=2\alpha<0\ 004$)

The mortality rate in connection with pregnancy and neonatal complications in Table VIII is the same for the groups in question although it must be pointed out that in reality the result for group B is better because 26% of the mothers in this group—as mentioned above—had pre-eclamptic toxaemia against 2% in group A

DISCUSSION

In the present series phenobarbitone administered orally to pregnant women for three days or more immediately before delivery reduced the various mortality rates by 50% or more If the mothers have not been treated it seems that phenobarbitone given as injections to the infant is valuable In this connection some questions concerning the drug will be discussed

Table VIII *Number of dead infants during the first 4 weeks*

	Group A Subgroup I (98 live born infants)	Subgroup II (49 live born infants)	Group B (19? live born infants)
Pregnancy complications	4	3	3
Neonatal complications	5	5	4
No demonstrable complications except low birth weight	19	8	1
Total	8	16	8

Risk of phenobarbitone treatment In a few cases it was necessary to stop the medication to the mothers because they developed a skin rash Some mothers complained of being sleepy and lazy Many times the latter disadvantage was caused by aversion to taking an old fashioned sedative If the tablets (100 mg daily) were called K 100 and the mothers were told that the drug was good for the child there were as a rule no complaints

The average Apgar scores 1 minute after birth were 7 9 in Group A and 7 6 in group B In group A 19% has Apgar scores 1 to 5 25% 6 to 8 and 56% 9 to 10 In group B the percentages were 19% 33% and 48% respectively These findings are similar to those published by Donvig et al in 1967 who compared the Apgar scores for two groups of infants delivered by Caesarean section The same kind of anaesthesia was used but in one group the anaesthesia was started with a barbiturate embomalum (250 mg or less intravenously) The embomalum anaesthesia decreased the number of infants with the highest Apgar scores increased the number of infants with the middle scores while the number of infants with the lowest Apgar scores was unchanged The authors concluded that the doped infants require careful attention after delivery particularly in the form of artificial respiration They also wrote that the Apgar score appears to be less useful as a prognostic indicator when embomalum has been administered to the mother In 1968 Secher & Wilhjelm (29) were of the opinion at the use of barbiturates for induction in obstetri anaesthesia increases the survival rate for in ants delivered by Caesarean section

No side effects have been observed in the neonatal period In particular there was no bleeding during the neonatal period as notified by Mountain et al (25) and Evans et al (12) Dortmann et al (9) did not find any influence on the blood clotting factors It is routine procedure in our department to give all infants 1 mg intramuscularly of phytomenandione immediately after birth

In 1961 Brazelton wrote that in a group of children whose mothers received more than 150 mg of barbiturates as early as 1 hour and not more than 6 hours prior to delivery there was a 5 days interval before 85% of their daily feedings were successful This was in contrast to infants whose mothers received 60 mg of barbiturates or less or nothing at all where there was a 4 days interval The usual period of disorganization (24 to 48 hours) seemed to be prolonged for 1 to 2 days if the mothers had re ceived 150 mg of barbiturates or more Simil observations have not been made in our depar ment but then the problem has not been systema cally examined

Desmond et al wrote in 1972 that withdraw symptoms starting from 30 minutes to 10 days po partum and lasting for 2–6 weeks occurred in newborn infants whose mothers had been given daily dose of from 90 to 120 mg of phenobarbito for at least 12 weeks prior to delivery The infan had poor postnatal weight gain as well as hypere citability and restlessness Although they appeare voraciously hungry feeding was frequently fo lowed by gagging and vomiting Similar dramat symptoms were never observed in our departmen

The matter of congenital malformation as a co sequence of phenobarbitone treatment to pregna epileptics has been taken up during recent yea (24 23) The general opinion is that the probabili of having a malformed child (most often cleft li with or without palate) appears to be two to thr times greater in epileptic women receivir anticonvulsant drugs Untreated epileptic mothe have a malformation rate not significantly differe from the control population (survey by Hill) Oth authors find however that the matter has not bee fully clarified as the articles published so far do n give sufficient information on the degree of epileps in treated and non treated mothers (30)

In the present maternal administration o phenobarbitone was not started until the last 1 weeks of pregnancy except to epileptic women

Benefit of phenobarbitone treatment In additio to the favourable effect on the infant mortality rate the phenobarbitone treatment presents other ad vantages In two papers published in 1968 (34 35 I have shown that administration of phenobarbitone to the pregnant woman or to the newborn or t both reduces the incidence of infants wi hyperbilirubinaemia (≥10 mg per 100 ml) The favourable result has been confirmed by seven authors (21 33 26 40 10 32 39 11 13 41 4 9 15)

Other authors (22 6 19 31) have reported th they have been unable to find any such effect o phenobarbitone but here it should be taken in consideration that they did not begin treatment un the infants had become jaundiced and that the was administered orally

Action of phenobarbitone Hepatic micros

enzymes situated in the smooth endoplasmic reticulum of the liver cells are responsible for the metabolism of endogenous and exogenous compounds. Administration of various drugs can stimulate the quantity and activity of these enzymes, so-called enzyme induction. Remmer (27, 28) and Conney (4) have independently discovered that barbiturates are enzyme inducers (5). This induction increases the hepatic microsomal enzyme uridine diphosphoglucuronyl transferase responsible for the glucuronide conjugation of bilirubin (3). Recently it has been shown (16) that phenobarbitone given to the mother before delivery or to the infant from the time of birth enhances bilirubin clearance in the newborn infant.

Another favourable effect of phenobarbitone should be mentioned. Animal experiments have shown that the survival time of hypoxic animals previously anaesthetized with different barbiturates is longer than that of unanaesthetized animals exposed to the same low oxygen concentration. Barbiturates cause a reduction in the oxygen uptake by cerebral tissue. This depressant effect of barbiturates on cerebral oxygen consumption causes a greater resistance to hypoxia so that the tolerance of the brain is increased (39).

Whether other factors are involved in the reduction of the infant mortality rate as observed by us can hardly be decided at the moment.

Nor can it be decided whether phenobarbitone is the best possible barbiturate and perhaps quite different drugs may be a possibility. Thus Thompson et al. (34) showed that dicophane could reduce the plasmabilirubin of a 17 year old boy with familial unconjugated non haemolytic jaundice.

CONCLUSION

Since only 5 to 10 % of pregnant women give birth to low birth weight infants it is an unrealistic thought that phenobarbitone should be given to all pregnant women during the last three months of pregnancy. But to my mind it would be a good idea to treat high risk pregnancies as for instance women with a history of a former stillborn infant, former premature delivery, pregnancy complications, especially pre-eclamptic toxaemia and hypertension and planned induction of labour before the 37th week. If treatment has been given during the last three days or more before delivery it would be unnecessary to treat the infant. If the mother has not received phenobarbitone or received it for less than three days before delivery or administration was stopped prior to the last three days of pregnancy it is recommended to treat the infant *immediately* after birth and during the next three days of life.

The dosage to the mother should as a rule be 100 mg per 24 hours. For the infant the dosage recommended is mentioned above under Material and Treatment.

It is possible that the mortality rates could be still more improved by a supplementary use of betamethasone therapy to the pregnant woman as proposed by Liggins & Howie (20) who have found a favourable effect on RDS by using this therapy.

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BLOOD FLOW IN MYOMATOUS UTERI AS MEASURED BY INTRA ARTERIAL 133XENON

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tract Uterine blood flow has been studied using a arterial 133Xenon Compartment analysis was used calculation of blood flow from the wash-out curves In myomatous uteri the mean blood flow was 11 6±1 70 min 100 g In 8 control cases the mean blood flow ; 20 1±2 27 ml min⁻¹ 100 g The difference is istically significant on the 1% level From the present dy it cannot be decided how the uterine blood flow is tributed between myomata and surrounding myo trium

e vascularization of uterine myomata has been subject of several studies The well known idency in these tumors to undergo degenerative anges has been regarded the result of insufficent od flow

Myomata also have an influence on the vascula e of the surrounding myometrium probably ereby also affecting blood flow in other parts of uterus Abnormal uterine bleeding in connec n with myomata has been ascribed to such vascu effects

Injecting radio-opaque medium into surgically moved uteri Sampson (8) found varying vascular in myomata depending on the size of the tumor nall tumors were usually found less vascular than ger ones Age was also found to influence the scularity uteri and myomata of older women owing lesser vascularity than those of younger men In degenerating myomata a varying picture s found Holmgren (6) using a similar technique died different types of degenerative changes He ssed the difference between the hydropic rosis rich in vessels and the dry necrosis poor vessels Faulkner (2) could not confirm this dif nce He found as a rule a very rich arterial work but very few veins in the myomata The venous network never reached the density of that of normal myometrium

Fernstrom (3) used pelvic arteriography and in his radiographs he could not differentiate between arteries in the capsule and within the myoma nam ing them all tumor vessels The density of tumor vessels was related to the size of the tumor Smaller myomata had very few or no blood vessels and larger myomata were as a rule richer in tumor ves sels

Farrer Brown et al (1) used a micro-radiographic and histological technique and found that the in trinsic blood supply of a myoma had no regular pattern The arterial network was found to be less dense than in the surrounding myometrium They did not mention myomata richer in arteries than the surrounding myometrium The venous pattern was even more sparse than the arterial

Studying the influence of myomata on the total uterine vasculature Sampson (9) found that some myomata were associated with a dilatation of uterine veins He interpreted this to be the result of increased arterial inflow caused by the myomata The association between excessive uterine bleeding and changes in the myometrial and endometrial venous plexuses is pointed out by Farrer Brown et al (1) By compressing veins in their surrounding myomata cause congestion When congestion oc curs in veins draining the endometrium abnormal uterine bleeding easily results

From morphological studies it is thus obvious that uterine myomata affect uterine blood flow by compressing surrounding vessels and by deriving their blood from branches of the uterine artery

Information on intrinsic arteries seems con tradictory From available morphological data it is

difficult to draw any conclusions concerning the amount of blood flowing through myomata and myomatous uteri. The only study giving quantitative values for blood flow in myomatous uteri known by the author is the work by Klingenberg (7).

Using an electromagnetic flowmeter placed around one of the uterine arteries he reports blood flow in 10 cases, 9 of which were myoma cases. He found rather constant values irrespective of uterine weight, i.e. the heavier the uterus the lower the blood flow per unit weight. He suggests that this is the result of lower blood flow in myomata than in myometrium.

Since very little quantitative data on blood flow in myomatous uteri exist it was considered of interest to apply the isotope clearance method to elucidate the conditions further.

METHODS AND MATERIAL

The theory of the isotope clearance method and the technical details in applying it to the study of uterine blood flow has been described in previous papers (4, 5). The intra-arterial injection technique described there was used. Conventional graphical separation of curve components was performed. These components were then used for the calculation of total blood flow within the isotope labelled region. This value is in the following called uterine blood flow (UBF) and has been calculated according to eq. 1.

$$UBF = \frac{100}{\sum_{1} \frac{A}{F}} \qquad (1)$$

A_i stands for percentage isotope in each compartme[nt] when elimination starts. F_i stands for blood flow in ea[ch] compartment calculated from curve half times and ex[-] pressed in ml min^{-1} 100 g^{-1}.

The percentage weights of compartments have be[en] calculated according to eq. 2.

$$W_i = \frac{\frac{A_i}{F_i} 100}{\sum_{1} \frac{A_i}{F_i}}$$

where W_i stands for percentage tissue weight perfuse[d] blood flow F_i. When three curve components [were] *identified the percentage weight of the well perfu[s]ed* [frac]tion of tissue has been calculated according to the fo[llow]ing modification of eq. 2.

$$\text{Percentage weight of well perfused tissue} = \frac{\left(\frac{A}{F_1} + \frac{A_2}{F}\right)}{\frac{A}{F_1} + \frac{A}{F_2}}$$

In all calculations of blood flows a partition coeffi[cient] of 0.7 was used.

Two groups totalling 15 patients were studied. I[n all] cases a total abdominal hysterectomy was performed. [One] group included 7 patients with uteri containing mul[tiple] myomata. In all these cases the indication for surg[ery was] uterine myomata causing abnormal uterine bleedin[g or] symptoms of compression.

The other group of 8 patients was used as control group was heterogeneous as to diagnosis and indicati[on for] surgery. Patients with one single myoma not exceedi[ng] cm in diameter were accepted in this group. No case [of] cancer or precancer of the endometrium were includ[ed in] either group.

The results are given in the text as mean va[lue] ±standard error of the mean. For statistical evalua[tion] the Wilcoxon rank sum test was used.

Table I. *Myoma cases*

Patient no	Age	Pregnancies	Phase of cycle	Blood flow in ml min^{-1} 100 g^{-1}: UBF	Quick comp	Slow comp	% well perf tissue	Remarks
1	37	1–0–0	Prolif	10.5	32	6.5	15.8	
6	52	2–1–0	Prolif	7.1	13.9	6.1	13.3	
12	41	1–1–0	Prolif	14.6	44.1	10.1	13.2	
13	46	–1–0	Secr	15.6	30.3	4.2	43.3	
14	50	3–1–0	Secr	17.1	34.7	4	47.5	
19	43	2–0–0	Prolif / Secr	12.7	5.5	4.4	30.3	Very quick comp 162 ml min^{-1} 100 g^{-1}
24	39	1–2–0	Secr	3.5	16.2	2.1	9.9	^{85}Kr instead of ^{133}Xe
Mean	44.0			11.6	28.1	5.3	24.1	
S.E.M.	1.95			1.70	3.69	0.89	5.06	

First figure: number of deliveries, second figure: number of abortions, third figure: number of extrauterine pregnancies.

Table II *Control cases*

Patient no	Age	Diagnosis	Pregnancies*	Phase of cycle	Blood flow in ml min 100 g			% well perf tissue	Remarks
					UBF	Quick comp	Slow comp		
5	35	Menorrhag	4-0-0	Secr	19 7	4?	10	30 4	
9	37	Menorrhag	3-0-0	Oral contraceptives	14 9	3? 4	4 1	38 3	
5	33	Endometriosis Dysmenorrhoea	?-0-0	Secr	2 1	40 4	7 8	27 9	Very quick comp 121 ml min⁻ 100 g
6	44	Menorrhag	3-1-0	Prolif	18 9	40 4	6.3	36 9	
7	38	Meno-metrorrhagia	?-0-0	Prolif	36 1	24 2	3 9	41 6	Very quick comp 3.5 ml min 100 g
1	46	Meno-metrorrhagia	2-0-0	Prolif	17.2	30 3	9 3	49 3	
2	43	Varicocele pelvis	3-0-0	Prolif	15 7	3 3	3.5	17.8	Very quick comp 179 7 ml min 100 g^{-1}
3	43	Ca cervicis	2-0-0	Secr	16 1	32 3	6 2	37 8	
Mean	39 9				20 1	34 3	6 4	32 5	
S E M	1 56				2 27	2 02	0 82	3 36	

* First figure number of deliveries second figure number of abortions third figure number of extrauterine pregnancies

RESULTS

The cases are presented together with results in Tables I and II In all cases multi-exponential wash-out curves were obtained In three cases in the control group and one case in the myoma group an initial very quick elimination with a half time of 0 14–0 40 min was observed The other two curve components showed small differences between the groups the mean blood flow corresponding to the quick component being 28 1±3 69 ml min^{-1} 100 g^{-1} in the myoma group and 34 3±2 02 ml min^{-1} 100 g in the controls and for the slow components 6 3±0 89 and 6 4±0 82 ml min^{-1} 100 g^{-1} respectively The groups are not statistically separated on the 5% level

When percentage tissue weights corresponding to the quick and very quick components are added the value in the myoma group is 24 1±5 06% and of the controls 32 5±3 36% The difference is not statistically significant UBF calculated according to eq 1 was 11 6±1 70 ml min^{-1} in the myoma group and 20 1±2 27 in the control group This difference is statistically significant ($p<0\ 01$)

If the groups are subdivided according to phase of menstrual cycle no clear pattern is seen There is a slightly higher mean age in the myoma group This difference however is not statistically significant

DISCUSSION

Uterine blood flow is probably affected by a multitude of factors Examples of such factors are age hormonal status parity uterine contraction local infections and tumors general and local hemodynamic factors such as arterial and venous blood pressure This study concentrates of one of these factors—the effect of uterine myomata However the other factors are affecting the result of the study causing a considerable spread of values

In the present method for study of uterine blood flow the whole organ is probably not labelled with isotope The isotope injection is made into the right uterine artery There exist numerous anastomoses with the contralateral side but in all probability the right half of the uterus is preferentially labelled It must thus be pointed out that the UBF is in fact blood flow in the region labelled with isotope The conclusions concerning the flow differences between myoma and control cases are not affected by

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A PROSPECTIVE STUDY OF DRUGS AND PREGNANCY

I Psychopharmaca

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stract A prospective study has been performed on the : of psychopharmaca during 6376 pregnancies and its relation to certain socio medical variables and preg ncy outcome An association between drug use and er miscarriage or legal abortion was demonstrated and conceivably due to an increased use of such drugs in wanted pregnancies No indication of an association tween drug use and birth of a dead or defective infant is found Pregnancies where psychoph irmaca were ed during the first trimester had on average a longer ration than pregnancies where such drugs were not ed but birth weight of full term infants was not af cted

sperimental studies on laboratory inimals and astic clinical experience especially the alidomide tragedy have taught us that drugs and her chemicals when given to the m iternal or nism c in damage the embryo In well controlled imal studies such effects can be relatively easily monstr ited They c in be recorded by one or ore of the following parameters rate of major and inor structural malform itions of the voung rate of illbirth or neonatal death miscarriage rate weight live born young Similar effects should be looked r in the evaluation of possible embryopathic ef ts of drugs on the human embryo and fetus

Such analysis will however be complicated by any sources of variation In a well planned animal periment the distribution of individuals to groups eiving the drugs in various dosage or serving as ntrols is randomized This is not the case in clini l studies The presence of diseases or complaints otiv iting the administration of drugs distinguishes drug consuming and the control groups Other factors may also influence drug usage e g social class civil status age psychological factors

The mere ascertainment of the fact that a certain woman has used a specific drug during a certain p irt of her pregnancy presents difficulties Re trospective data on drug consumption obtained af ter the end of the pregnancy are liable to bias A woman who has had a dead or malformed child or has experienced an unwelcome miscarriage has a stronger reason to search her memory for events which could explain the disaster e g drug usage than a woman who has had a normal living child To a certain degree these fallacies can be balanced by close scrutinity of written records including prescriptions An elegant study by Nelson & Forfar (11) has used this technique Another method is to only use information collected prospectively False information may be included but data will be little biased by outcome of the pregnancy Such prospec tive studies must necessarily result in much smaller series of malformed infants th in a retrospective study can This can be partly balanced by using other parameters like miscarriage rate and birth weight for the evaluation of drug effects Recent publications on prospective studies on drug effect are those of Crombie *et al* (3) and especially Vil lumsen (14) The latter study was performed on 9006 hospital births in Copenhagen and discusses —among many other features—drug use in relation to malformation of the infant

Special interest has been paid to psychopharmaca in this connexion Thalidomide the best known and perhaps strongest teratogenic drug active on hu



Fig. 1 Percentage women using psychopharmaca during different months of pregnancy according to pregnancy outcome ——=miscarriage - - - =induced abortion =live infant — — —=dead infant

mans belonged to this category psychopharmaca pass the blood-brain barrier and therefore probably also the placental barrier these drugs are often used in early pregnancy and their use is not always justified by the signs or symptoms for which they are prescribed New interest was stimulated in this group of drugs when McBride (9) claimed that an antidepressive drug imipramine was markedly teratogenic for humans Many authors have contradicted that conclusion but some support was given by Idanpaan-Heikkila & Saxen (5) for at least a weak teratogenic action of tricyclic antidepressive drugs

The present paper is the first in a series describing results from a prospective study on drugs and pregnancy The data were collected during 1963–65 Later contributions will discuss anti-emetic drugs hormones and a number of miscellaneous drugs

MATERIAL AND METHODS

Some information on the present study has been given earlier (4 6 7) The material is based on questionnaires filled in by pregnant women in the city of Malmö during 1963–65 Every woman who was found to be pregnant was asked to complete a questionnaire which was returned within a few days In this questionnaire information from the last menstrual period up to the first visit to the doctor was given A new questionnaire was then handed over to cover the period up to her next visit to the doctor and so on—the entire pregnancy was usually covered by four such questionnaires Part of the information is thus retrospective because it was given after the event but it was usually collected before the outcome of the pregnancy was known

All gynecologists in Malmo inside and outside the hospital were engaged in this study Information obtained from the questionnaires was supplemented with data from hospital records

A total of 6 913 pregnancies were recorded but only 6 376 could be followed (92.2%) The outcome of the pregnancy was evaluated as miscarriage (up to the 7th gestational month) 448 induced abortion (legal or known criminal abortions) 158 extra-uterine pregnancy birth of a child 5 753

All living children were carefully investigated by a pediatrician after birth and were followed to about one year old at the child health centres Autopsy was performed on infants and the age at death was recorded The presence of major and minor malformations was recorded for all infants (4) Birth weight and placenta weight were also recorded

Information on drug use was obtained mainly from the above mentioned questionnaires sometimes supplemented from hospital records etc The (approximate) time of intake of each drug used was recorded and referred to the gestational month of the pregnancy

On the first questionnaire the woman was asked if the pregnancy was wanted or unwanted Records of major and minor diseases were kept The woman's age parity civil status and social class were recorded Social class was evaluated by the health insurance class of the woman or her husband whoever had the higher As health insurance is compulsory in Sweden and the sum paid per day is proportional to the person's income this gives an estimate of her socio-economic level

RESULTS

Spontaneous and induced abortion

The frequency of women reporting to have used psychopharmaca during the various gestational months (up to and including the seventh) is shown in Fig. 1 in relation to pregnancy outcome *Women who will later miscarry report* a higher rate of psychopharmaca use during the first months of pregnancy than do women whose pregnancies end in the birth of an infant dead or alive During the first month i e before the woman knows she is pregnant 42 of the 417 women who will later miscarry report that they used psychopharmaca In

Table I *Frequency of diagnosis of psychoneurosis*

Outcome of pregnancy	No of diagnosis	Total no of women	% of women with diagnosis	χ^2
Spont abortion	10	448	2.2	8.7
Induced abort	28	158	17.7	35.4
Childbirth	48	5 753	0.8	–

Comparison with women who gave birth to a child

control group of all women who bore a child 328 among 5 753 used psychopharmaca This difference is highly statistically significant ($\chi^2=13.1$ at 1 d f $P<0.001$) During the next few months there is still a statistically significant difference ($\chi^2=10.7$ and 6.2 $P<0.001$ and $0.02<P<0.01$ resp) After the fourth month there is a sudden increase in psychopharmaca consumption among women who will miscarry There are only 81 women left in this group during the fifth month but 14 of these report use of psychopharmaca This differs with high statistical significance from the rate among women who will bear a normal child—301 among 5 753 such women used psychopharmaca during the fifth month of gestation ($\chi^2=22.7$ $P<0.001$)

Women who will later have an induced abortion show an increased rate of psychopharmaca consumption especially during early pregnancy There is a marked decrease during the fifth and sixth months but relatively few women enter this group at that time During the fifth month 98 women will still have an induced abortion and 20 report the use of psychopharmaca during that month When compared with the figures for the third month (39/122) the difference appears to be marginal ($\chi^2=3.7$ at 1 d f P near 0.05)

Psychopharmaca use and medical and social variables

The most obvious disease resulting in a prescription of psychopharmaca is psychoneurosis Table I gives the frequency of this diagnosis among women who will have a spontaneous abortion an induced abortion or give birth to a child As is seen from this Table there is a significant increase in the incidence of this diagnosis among women who will have a later abortion—whether spontaneous or induced The latter is quite reasonable the former may be due to the fact (7) that women who will have a spontaneous abortion to a higher degree experience unwanted pregnancies than women who will have a child

Psychopharmaca are prescribed and used also in the absence of a manifest psychoneurosis One possibility is that a woman who chances to have an unwanted pregnancy would be more prone to use a sedative or an antidepressant drug Table II shows an analysis of this phenomenon A statistically significant over representation of psychopharmaca usage during early pregnancy is obviously present among women with an unwanted pregnancy Such a pregnancy is apt to end with an induced abortion—some of which may be taken as spontaneous—which will result in an apparent association between drug consumption and miscarriage This phenomenon resembles that found earlier (7) on the relationship between smoking and abortion

The desire for pregnancy is associated with a number of other characteristics the most obvious one being civil status A comparison was made of psychopharmaca usage during early pregnancy in women who ultimately bore a child 4 015 were married at LMP and 844 were unmarried In the former group (92% of these women reported a wanted pregnancy) 14.9% used psychopharmaca during the first trimester but in the latter group only 12.7% did so This difference is not statistically significant ($\chi^2=2.8$ at 1 d f) but at any rate the marked difference in percentage of unwanted pregnancies is apparently counter balanced by other differences between the two groups of women which influence use of psychopharmaca

Fig 2 shows the use of psychopharmaca in women belonging to different social classes as judged by income There is a slight trend to an increase in drug use with income class but this is of limited significance A test of the trend in the frequency table according to Maxwell (8) gives a $\chi^2=3.9$ for first trimester psychopharmaca consumption ($P=0.05$) and $\chi^2=2.2$ for total psychopharmaca consumption (N S) This correlation is however also

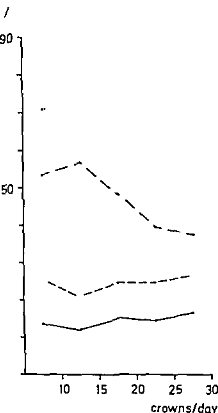


Fig 2 The relation between some variables and social class estimated as crowns per day in health insurance for woman or her husband whoever had the highest sum ——=first trimester drug 777=second third trimester drug =wanted pregnancies – – – –=smokers

influenced by the desire for pregnancy As is seen in this Figure the percentage of wanted pregnancies is higher in the higher income groups than in the wer Therefore a decrease in psychopharmaca age would be expected instead of the possible light increase recorded With a knowledge of the percentage of wanted pregnancies in each social class and the mean percentage of women using psychopharmaca (Table II) the expected number of such women in each social class can be calculated supposing no other factor influences drug use The following result is obtained class 0–10 113 expected 93 found class 11–15 116 expected 85 found class 16–20 226 expected 225 found class 21–25 169 expected 170 found and class 26–30 128 expected and 142 found A χ^2 analysis gives $\chi^2=13\ 7$ at 4 d f $0\ 01 > P > 0\ 001$ Thus there is a relative increase in the use of psychopharmaca when the changes in degree of desire for pregnancy are taken into consideration in the higher income groups This phenomenon may be the same as that recorded for civil status By contrast there

Table II *Use of psychopharmaca before the 4th gestational month and desire for the pregnancy*

Desire for pregnancy	Total no of women	No of women using psych pharm	Percentage women using psych pharm
Wanted	5 136	651	12 7
Not wanted	1 097	253	23 3
Not stated	159	–	–

$\chi^2=81\ 2$ at 1 d f $P<0\ 001$

is a marked decrease in smoking frequency which reflects the changes in frequency of unwanted pregnancies

The mean age of all women using psychopharmaca during the first trimester is 28 04±0 19 years that of all women who do not report psychopharmaca consumption is 26 21±0 08 This difference is statistically highly significant ($t=8\ 9$ $P<0\ 001$) The mean age of women using barbiturates during the first trimester is 28 0 years that of women using meprobamate is 27 9 and that of women using hydroxizine is 29 6 years

Social class and age are also associated The mean ages in different social classes are 0–10 24 26 years 11–15 22 61 years 16–20 26 78 years 21–25 28 47 years 26–30 30 76 years With a knowledge of the number of women using psychopharmaca and belonging to the different social classes the expected mean age of all women using these drugs can be calculated and is found to be 26 9 years which is still below the actual mean age of 28 04 ($t=3\ 8$ $P<0\ 001$) It thus appears that desire for pregnancy age social class and/or civil status all influence use of psychopharmaca during early pregnancy

Malformation rate

Fig 3 presents the use of psychopharmaca during different months of pregnancy comparing women who gave birth to non malformed infants to infants with minor malformations only and to infants with major malformations Fig 4 compares in a similar way two groups normal infants and infants dead or malformed (=perinatal pathology) No obvious difference exists between the different groups—if anything the total perinatal pathology group appears to lie below the group of normal infants though this is not statistically significant

Table III compares the three different groups

from another aspect incidence of psychopharmaca use at any time during the first trimester The incidence of gross major malformations is slightly higher than in the control group but this difference can well be random ($\chi^2=1.0$ at 1 d f N S) The two other groups of malformations (minor and insignificant major) are even slightly decreased The Table also summarizes the distribution of pregnancy outcome after the use of some specific psychopharmaca—alone or together with other drugs The number of infants born with defects lies well within expected limits The actual numbers are small however Even for meprobamate which was used during the first trimester by 263 women who later had a child the recorded number of infants with major malformations could be a random minus variation at a major malformation rate of 7 2%—that is double the control level—at a probability of $P=0.05$ These observations thus do not exclude a teratogenic effect of the drugs but give no positive support for it

Table IV presents a slightly different approach to



Fig 3 Percentage women using psychopharmaca during different months of pregnancy Comparison between women who had non malformed infants (——) infants with minor malformations (– – –) or infants with major malformations ( )

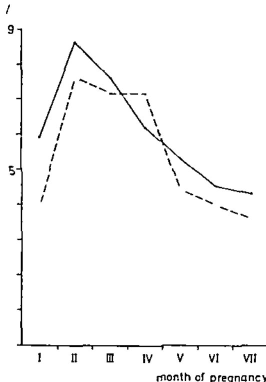


Fig 4 Percentage women using psychopharmaca during different months of pregnancy Comparison between living normal infants (——) and the group of perinatal pathology i e stillbirths or infants with major malformations (– – –)

the material 194 records of pregnancies that ended with the birth of an infant with a major malformation were compared with 194 matched controls the latter were chosen from the first suitable questionnaire with the nearest consecutive number to each one in the study group A similar series was collected of 93 infants who died before the age of one year but who had no malformation—53 of these were stillborn Matched controls were selected as above The first trimester use of psychopharmaca in general and meprobamate in particular is shown in the Table—the series has also been subdivided according to the occurrence of some different malformations The expected number of users calculated from the total series (5 753 births) is also given

In this series use of psychopharmaca occurred more often in the malformation group than in the control group ($P=0.05$) There were no differences between the group of dead infants and its control group There are however lower incidences in all

Table III *Malformations and stillbirths among infants to women who used psychopharmaca during pregnancy*

Infant category	Total number	All psych pharm Trimester 1st	2nd–3rd	Mepro bamate	Barbi turate	Chlor diaze poxide	Hydroxi zine	Imi pramine	Other anti depressive drugs
All	5 753	815	456	263	372	89	16	13	16
Not malformed	5 002 (87.0%)	710 (81.9%)	390 (85.5%)	233	316	82	14	9	15
Minor malformation	551 (8.6%)	74 (8.5%)	49 (10.8%)	18	43	5	2	3	0
Insignific major malf	105 (1.7%)	14 (1.6%)	9 (2.0%)	6	4	2	0	0	0
Gross major malform	95 (1.5%)	17 (2.0%)	8 (1.8%)	6	9	0	0	1	0
Stillbirth	68 (1.1%)	14 (1.6%)	3 (0.7%)	5	6	1	0	1	0

groups except that of malformed infants when comparison is made with the total series The reason for this is not clear

When the group of malformed individuals is broken down according to the malformations present it is found that no major deviation occurs from expected numbers with one possible exception congenital heart defects This may well be random however The slightly increased incidence at Mb Down would fit with the higher mean age at child birth for this group

Pregnancy length and birth weight

Table V shows the distribution of length of preg- nancy among normal infants born to women who used psychopharmaca during the first trimester or during the second and third but not the first trimes- ter and those born to women who did not use psychopharmaca There is a possible difference be- tween the groups with a longer duration when the drugs had been used during the first trimester It necessitates comparisons of birth weight being car- ried out at the same gestational age Table VI show

Table IV *Number of women using psychopharmaca in general and meprobamate in particular spec during the first trimester Infants with major malformations and matched controls infants without malformations but dead within one year with matched controls*

Expected numbers calculated from the incidence of psychopharmaca users in the total material of women giving birth to non malformed infants (710/5 002) or from all controls

Infant group	Total number	No using psycho pharmaca	Expected number from total material	No using meprobamate
Major malform	194	28	27.5	10
Controls to major malf	194	14	27.5	6
Dead but not malformed	93	9	13.2	3
Controls to dead but not malformed	93	9	13.2	5
Dead and/or major malf	287	37	40.7	13
All controls	287	23	40.7	11
Specific malformation types			*Expected no from all controls*	
C N S malform	11	2	0.9	2
Cleft lip and/or palate	10	3	0.8	0
Cong heart malformation±other malf	35	5	2.8	0
Hypospadias	15	2	1.2	0
Cong dysplasia of hip	37	1	3.0	0
Multiple malf	10	1	0.8	0
Mb Down	10	3	0.8	2

Table V *Duration of pregnancy when psychopharmaca were used during the first trimester during the second or third but not the first trimester and when such drugs were not used at all*

Expected numbers (calculated for each sex separately) given within parentheses for pregnancies shorter or longer than 38–42 weeks

	Total number	Duration of pregnancy less than 38 weeks	38–42 weeks	more than 42 weeks	χ^2 (4 d f)
Boys					
Drug first trimester	355	26 (27)	308	21 (15)	
Drug 2nd–3rd trimester	186	18 (14)	166	2 (8)	8 1( )
No drug	1 848	137 (140)	1 634	77 (77)	
Girls					
Drug first trimester	332	19 (22)	296	17 (11)	5 3 NS
Drug 2nd–3rd trimester	187	13 (13)	170	4 (6)	
No drug	1 858	129 (1 6)	1 673	56 (60)	

χ^2 between drug groups within sexes = 13 4 at 8 d f
NS = non significant

The weight distribution among infants born within 2 weeks from expected date of birth (38–42 weeks of pregnancy) No effect of use of psychopharmaca on birth weight can be found

DISCUSSION

The use of psychopharmaca during pregnancy is probably dependent on many different factors some of which have been analysed in the present study The desire for the pregnancy the civil status of the woman at LMP the socio-economic class of the woman and her age are four factors which have been shown to affect drug use and these four factors are themselves obviously interacting Some of them are known to be associated with pregnancy outcome especially with respect to stillbirth rate (1)

Psychopharmaca are primarily used for mental diseases but are also prescribed for various other complaints An unwanted pregnancy would be expected to favour the use of such drugs This was also shown to be the case As was demonstrated

Table VI *Birth weights among non malformed infants born within 2 weeks before or after expected birth date (38–42 weeks pregnancy) when the woman had used psychopharmaca during the first trimester during second or third but not the first trimester or had not used such drugs at all*

	Total number	Birth weight kg <2 5	2 5–3	3–3 5	3 5–4	4–4 5	>4 5	χ^2 (10 d f)
Boys								
Drug first trimester	308	7	23	90	125	54	9	
Drug 2nd–3rd trimester	166	4	14	50	63	30	5	5 9 NS
No drug	1 634	8	142	563	600	250	51	
Girls								
Drug first trimester	296	7	41	13	89	18	9	
Drug 2nd–3rd trimester	170	7	20	64	51	5	3	18 2
No drug	1 673	35	253	662	551	141	31	

χ^2 between drug groups within sexes = 4 1 at 0 d f NS
0 1>P>0 05
NS = non significant

earlier (7), women who will later miscarry report a higher proportion of unwanted pregnancies than women who will later have a child and so an association between use of psychopharmaca and miscarriage would be expected and is also found. The incidence of drug use is, however, already higher among the miscarriage group of women during the first gestational month, i.e. before the woman knows she is pregnant. Apparently, other factors—probably of a social nature—exist which are associated with the risk of an unwanted pregnancy and which also favour psychopharmaca consumption.

Unwanted pregnancies are, of course, more common among women who are not married at the LMP than among women married at the LMP. Civil status and the desire for the pregnancy should therefore be expected to affect psychopharmaca consumption similarly. On the contrary, women who are married at the LMP use more psychopharmaca during the first trimester than women unmarried at the LMP do. The effect of differences in desire for pregnancy must thus be balanced with other factors associated with civil status and leading to increased use of psychopharmaca. This is also illustrated in an analysis of the effect of socio-economic class on psychopharmaca consumption. In such higher classes (Fig. 2), the rate of wanted pregnancies increases. As could be expected (7) this is paralleled by a decrease in smoking frequency—as smoking is correlated with unwanted pregnancy. On the other hand, the use of psychopharmaca increases. From the calculations presented, it is likely that both age of woman and *another factor associated with civil status and* therefore with socio-economic class affect psychopharmaca consumption.

The increased use of psychopharmaca among women who will later miscarry is thus an effect of social factors and there are no indications that the use of such drugs in itself increases the risk of a miscarriage—a phenomenon exactly paralleling what was found for smoking (7). The late rise in psychopharmaca consumption noted for women who will have a late spontaneous abortion may perhaps be due to medication caused by signs and symptoms indicating the threatening abortion. It is, however, also interesting to note that the increased smoking among women who will have a miscarriage was mainly restricted to those who will have a late abortion (7). There are no indications of an association between use of psychopharmaca and the bi… of a dead or defective child. Richards (17) describe… an association between the birth of a child w… major malformation and the use of sedatives du… the first trimester. Crombie et al. (3) also found … excess of barbiturate prescriptions among wom… who will have a malformed child compared w… controls and the same finding was reported b… Nelson & Forfar (11). Villumsen (14) could not r… cord any effect of barbiturate or other psych… pharmaca on malformation rate. Belafsky et al. (… compared pregnancy outcome in 900 women w… used meprobamate during pregnancy with 50… other gravidas from the same region without findi… any adverse effects. The incidences of deform… infants recorded in both groups were so low, how… ever, that ascertainment of developmental defe… must have been inefficient. A lower abortion r… was described in the meprobamate group than in … control group, a finding at variance with ours.

No firm evidence for a teratogenic effect w… found in the present investigation. The use of p… chopharmaca is equally common in the group … women who will have an infant with some sort … malformation as in the control group of women w… will have a normal infant, and no differences co… be found between minor or major malformati… When women who gave birth to infants with ma… malformations were compared with matched c… trols, a difference just reaching statistical sig… cance was obtained with a higher incidence of d… use in the study group than in the control gro… The study group had an incidence, however, wh… agreed well with the overall incidence recorded … *the total series. Either the lower* drug use in t… control group was a random phenomenon—but th… is perhaps made less likely by the fact that f… further groups showed the same low incidence… the matching process resulted in a selection … non users. It is hard to understand how the … process would have occurred but seasonal va… one factor which can play a role as it is well kn… that some malformations show a seasonal patter… incidence. The difficulty in identifying any spe… drug or any specific malformation in the associa… tells against a true association between drug use … teratogenesis.

In experimental teratology, a drug can affect b… malformation rate and fetal growth. An effor… therefore made to compare birth weight in inf… born to women who used psychopharmaca …

nfants born to women who had not It was found hat pregnancy length may differ—there was a shift owards longer pregnancies when the woman had used such drugs during the first trimester If this is not a random finding it could be a drug effect Certain drugs—so far mostly anti inflammatory drugs have been discussed from this point of view—can inhibit prostaglandin synthesis and release 13) The use of such drugs during pregnancy could hrough this mechanism prolong gestation time 10) A sedative effect on hypothalamic centres and the posterior pituitary could also be a possible explanation for a drug effect Social factors which have been shown to be of importance for drug use g age and social class could perhaps also be of mportance in this respect

When birth weights were studied within one roup—non malformed infants born at term (38–42 weeks pregnancy)—no effect of psychopharmaca use on infant weight was found

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DISC ELECTROPHORETIC PROTEIN PATTERN OF CERVICAL MUCUS IN CASES OF HUMORAL SENSITIZATION AGAINST SPERMATOZOA

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bstract Midcycle cervical mucus samples from 70 fertile omen with negative and from 6 infertile women with ositive serum sperm agglutinating activity were sub cted to a qualitative protein analysis by the Ouchrlony technique to polyacrylamide (PAA) discelec ophoresis and after purification on spermatozoa they ere also run against rabbit antihuman serum in the aurell immuno-electrophoretic technique By the Ouch rlony method the main serum protein fractions were iown to occur also in cervical mucus No significant fferences could be found in the protein pattern of sam es from fertile and infertile females as detected by olyacrylamide (PAA) electrophoresis In all samples a lit protein fraction corresponding to serum albumin and band preceding the protein fra tion corresponding to rum prealbumin were observed In 2 samples from in rtile females it could be demonstrated that im unoglobulins occurring in the cervical mucus were di cted towards antigenic sperm components

here has been quite a lot of recent comment about e protein fractions secreted along with local body uids (8 9) The protein components of female geni l tract secretions are thought to be important in nnection with fertility The protein fractions hich occur in the cervical mucus of normal indi duals have been widely discussed by Moghissi & euhaus (10) Schumacher (14) and Odeblad (11) t no clear information is available about the pro in composition of cervical mucus with respect to fertility

In the present paper the protein pattern of cervi l mucus in selected cases of infertile women with trong humoral antiseminal activity are described

MATERIAL AND METHODS

rvical mucus samples from 6 infertile women present t agglutinating humoral antibodies against spermatozoa, determined by the Franklin & Dukes method using 1 4 serum dilutions and of 0 fertile women without humoral sperm agglutinating activity were collected at midcycle under identical conditions by mild uction with a syringe connected to a conical polyester tube The samples were stored at −70° and after thawing subjected to the follow ing procedure

1 All samples were subjected to discontinuous polyacrylamide (PAA) electrophoresis (Ornstein 1964 Davis 1964) using a 3½% stacking gel and a 7½% separating gel in tris glycine buffer pH 9 0 Vertical col umns of 4 7 mm inner diameter 60 mm length 40 mm running gel and a current of 5 mA per column were used The protein content was adjusted individually to a total applied protein content of 250–350 µg per column

2 The occurrence of serum proteins in the cervical mucus was detected by the qualitative immunoprecipita tion method after Ouchterlony 1964

3 For the specification of immunoglobulins identified with the Ouchterlonytechnique the cervical mucus sam ples from fertile women and women with humoral agglutinating activity against spermatozoa were purified on spermatozoa by affinity chromatography in a batch device and their antibody content and type determined with rabbit antihuman serum in the two dimensional im munoelectrophoresis (7)

RESULTS

The PAA pattern of cervical mucus from normal fertile women compared with the corresponding protein pattern in serum is demonstrated in Fig 1 In addition to the protein fractions electrophoreti cally corresponding to the gammaglobulins and haptoglobulins of the sera a protein band regularly occurs in cervical mucus which corresponds to transferrin-C of human serum In the typical locus of serum albumin two fractions of high density are detected in PAA electrophorographs of cervical mucus This pattern of the albumin with two major

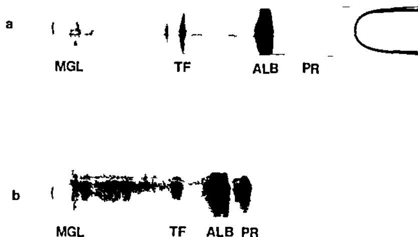


Fig 1 Comparison of PAA patt of serum (*top*) and cervical mu (*bottom*) of a normal fertile wo at midcycle

peaks was found only in 6 out of the 20 normal mucus samples examined In all these 6 cases the serum albumin fractions presented a single albumin peak (Fig 1) The most rapidly migrating protein fraction corresponds electrophoretically to the serum prealbumin fraction which occurred in all cervical mucus samples investigated In contrast to the serum prealbumin this band revealed considerable intensity in gels stained with Coomassie blue Furthermore in 4 cases an additional band occurred before the band corresponding to the serum prealbumin fraction which resembled serum urosomucoid

In 6 cases of cervical mucus from infertile women presenting a positive humoral sperm agglutinating activity the basical protein pattern a normal mucus samples was detectable In 2 cases considerable enlargement of the macroglobul fraction could be found (Fig 2) This may be rela to an artefact due to a poor mucus solubility specific gammaglobulin fraction cannot be dete by this particular technique

The Ouchterlony technique used revealed the o currence of the following protein fractions in cerv cal mucus from normal and infertile wome prealbumin albumin alpha acid glycoprotei

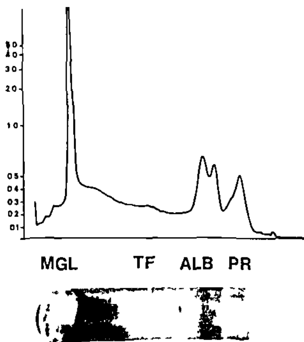


Fig 2 Densitograms of electrophoretic protein patter cervical mucus of 2 infertile w cervical mucus of 2 infertile w presenting 46 ± 6% and 28 + sperm agglutinating serum act

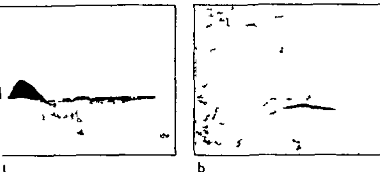


Fig. 3. Immunoelectrophoresis of an affinity chromatography purified cervical mucus sample from an infertile woman with sperm agglutinating serum activity (*a*) run against rabbit antihuman serum in comparison with a normal mucus sample (*b*).

ansferrin haptoglobulin immunoglobulins IgG id IgA. No immunoglobulins IgM, α2 macroglobu i or ceruloplasmin could be verified.

Applying crossed immunoelectrophoresis only in e 2 cases of sperm agglutinating serum activity a ecific antiseminal cervical mucus immunoglobu a defined by the typical localisation of the cor sponding precipitation band as well as by absorp- on studies could be demonstrated (Fig. 3). In ese 2 cases the antibody could be defined as IgA ile serum agglutinating antibodies could be ntified as IgM.

DISCUSSION

e results presented show a similar protein pattern cervical mucus and serum. Major differences re t from the occurrence of a split albumin fraction d the occurrence of a protein fraction preceding band corresponding to serum prealbumin. To knowledge neither phenomenon has been de ibed previously. No major differences could be ected between the protein pattern of the mucus nples from fertile and infertile women except for ases of infertile females. In these 2 cases a con rable increase in the protein fractions cor ponding to the serum gammaglobulin region ld be observed in the cervical mucus.

hese 2 cases however do not permit any reli conclusions. Protein analysis of cervical mucus been accomplished by numerous authors using rent separating techniques. Discelectrophoretic lies performed by Beier & Beier (9) revealed a ilar pattern as presented in this report. The au s however do not relate their results to infertil

the desired aim of cervical mucus protein yses in cases of female infertility due to or associated with serum sperm agglutinating activity has been to disclose an accumulation of antiseminal factors perhaps immunoglobulins in this local genital secretion.

Immunoglobulins however proved to occur almost constantly in cervical mucus (9).

Furthermore even major variation in immunoglobulin content of the cervical mucus would hardly give rises to a detectable alteration in electrophoretic patterns. Moreover as to PAA media some Igs have not always been found to migrate in the PAA gel concentrations commonly used. In addition it has not yet been demonstrated that immunoglobulins occurring in cervical mucus of women with serum spermagglutinating or immobilizing activity are actually directed toward antigenic sperm component. The last step of our studies attempted to clarify this question. Sperm specific immunoglobulin purified by affinity chromatography on spermatozoa in a batch device migrating into a rabbit antihuman serum showed one precipitation line that could be identified by localization and absorption as IgA.

To our knowledge this is the first evidence in favour of the idea that immunoglobulins found in cervical mucus are directed against sperm antigens. This is supported by the observation that such a positive reaction could not be found in the mucus of women without humoral sperm antibody activity when subjected to the same procedure (Fig. 3).

The results make it possible to measure the antiseminal portion of immunoglobulin occurring in cervical mucus. Shulmann (15) in 19 mucus samples from women with sperm agglutinating serum activity found 11 with a positive sperm agglutinating reaction using the Kibricktest and 10 by using Franklin & Dukes test.

These results accord well with our unpublished data on the occurrence of about a ten times lower sperm agglutinating activity in cervical mucus samples as compared with the serum The application of sensitive protein analytical methods as the Laurell immunoelectrophoresis and affinity chromatography (5) reveal effective antiseminal activities of cervical mucus uterine and tubal secretions undetectable with the current low sensitive serological methods

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STUDY OF THE SUPPRESSION OF LACTATION AND THE INFLUENCE ON BLOOD CLOTTING WITH BROMOCRIPTINE (CB 154) (PARLODEL®) A DOUBLE BLIND COMPARISON WITH DIETHYLSTILBOESTROL

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bstract Inhibition of lactation was studied in 38 uerperal women in a double blind trial to assess the effect f bromocriptine in compari on with diethylstilboestrol DS) Simultaneously the influence of both compounds n blood clotting was studied along with a control group f 0 women not receiving any medication Bromocriptine as given in a daily dose of 5 mg for 14 days and DS in a aily dose of 0 mg for 7 days followed by a placebo for a urther 7 days The first doses were not later than 8 hours fter delivery Both compounds showed an inhibitory ef ct on the onset of lactation and mammary congestion his inhibitory effect on both parameters was significantly i favour of bromocriptine during the last days of the eatment due to rebound in the DS group The romocriptine doses used (5 mg daily for 2 weeks) caused o objective side effects and no subjective restraint reatment with bromocriptine caused no untoward effect n the blood clotting while in the DS group a slower turn to normal antithrombin III could be observed Also i this group one case of thrombophlebitis occurred romocriptine can be administered to puerperal women or the suppression of lactation

nly a small choice of therapeutic measures were vailable until recently for the suppression of lacta on in puerperal women

Most commonly used is hormonal therapy with strogens and androgens in order to prevent pain il engorgement of the breasts However there is a finite risk of thromboembolic complications (12 5) The need for a potent and well tolerated drug to ippress lactation is therefore evident

Bromocriptine is the polypeptide ergot alkaloid Br alpha-ergocryptine The compound has a pecific inhibitory effect on prolactin secretion both rectly at the hypophyseal level by blocking prolactin release from the hormone producing cells (8 20 26) as well as indirectly by increase of hypothalamic prolactin inhibiting factor activity (32)

The antigalactic effect of bromocriptine has proved successful in several animal studies (2 9 10 25) and recently in puerperal women (4 23 24 29 31) The compound is also active in patients with galactorrhoeaamenorrhoea syndrome (5 7 14 16 17 21 22 28) as well as in male patients with galactorrhoea and impotence (1)

This report concerns the effect of bromocriptine and diethylstilboestrol (DS) on the onset of puerperal lactation and the blood clotting factors in a double blind trial

MATERIAL AND METHODS

Thirty-eight puerperal women entered this double blind comparative trial In addition to this a control group of 20 puerperal women was formed in order to obtain comparative values for blood clotting factors 0 women received CB 154 and 18 women were given DS Women with severe metabolic disturbances or with concomitant therapy e g corticoid thyroid anti thyroid therapy diuretics phenothiazines which might influence results of the study were excluded from the outset

There was no statistically significant difference between the mean values for the two groups as to age body height body weight parity duration of pregnancy duration of labour type of delivery (spontaneous/operative) systolic and diastolic blood pressure pulse rate as well as to the pretreatment values of the blood clotting tests (Table I)

The oral medication schedule was as follows

1 CB 154 capsules containing 2 5 mg of active compound one capsule orally in the morning and in the even

Table I *Basic data*

	CB 154 group	DS group	Test method	*P*
Age				
Mean value (years)	30 0	27 6	U Test	0.59 n
Extreme values	17–36	19–45		
Body height				
Mean value (cm)	151 1	167 1	U Test	0 3? n
Extreme values	156–178	167–178		
Body weight				
Mean value (kg)	72 8	74.5	U Test	0 43 n
Extreme values	58 2–94	61–88 5		
Number of pregnancies				
0	4	5	2I Statistics	0 86 n
1	5	3		
2	8	5		
3	1	2		
4	1	2		
5	1	1		
Mean value	1 7	1 8		
Duration of pregnancy (days)	258 1	259 8	U Test	0 83 n
Extreme values	210–290	210–280		
Duration of labour	7 4	6 7	U Test	0 54 n
Mean value (hours)	0 5–2? 5	1–45		
Type of delivery				
Spontaneous	18	16	2I Statistics	0 95 n
Perforation of skull (cranioclasis)	1	1		
Forceps	0	1		
Caesarean section	1	0		
Intervall between delivery—1st drug intake				
Mean value (hours)	4 5	4 4	U Test	0 99 n
Extreme values	1–8	0 8–8		

ing before meals during 14 consecutive days for a total of 28 capsules (70 mg)

2 DS capsules containing 10 mg of active compound one capsule orally in the morning and in the evening before meals during 7 consecutive days for a total of 14 capsules (140 mg) followed by further 7 days of placebo treatment administered in the same way

The 7 day administration of DS complies with the most commonly used medication schedule which is considered to be relatively safe regarding thromboembolic complications

All capsules were identical in appearance The allocation of the patients to the two treatment groups was done with the help of a randomisation list The first dose of drug was given not later than 8 hours after delivery

The patients were examined daily during their stay in hospital by both doctor and midwife Examinations by doctor were performed on each patient at the beginning and on day 14 of the treatment The following effects were assessed and scored Mammary secretion mammary con

Table II *Scoring system for determination of mammary secretion mammary congestion occurrence of side effects involution of uterus and overall assessment*

Score	Mammary secretion (by palpation)	Mammary congestion	Side-effects
0	No milk	Absent	Absent
1	Some drops	Slight	Slight
2	Slight outflow	Moderate	Moderate
3	*Stream of milk*	Severe	Severe
	Involution of uterus	Overall assessment	
0		No effect	
1	Poor	Poor	
2	Good	Good	

Table III *Prevention of mammary secretion*

roup		Treatment day				
		1st	6th	1?th	13th	14th
B 154	Secretion/Total no of pat	0/?0	3/20	1/20	1/?0	2/20(*)
S	Secretion/Total no of pat	1/18	0/18	8/18	7/18	6/18

) $P<0\ 1$ $P<0\ 05$ $P<0\ 01$

stion involution of uterus occurrence of side effects eneral assessment by doctor midwife and patient The oring are shown in Table II

The side effects which were recorded were either bserved changes which were uncommon in puerperal omen or subjective complaints spontaneously men oned by the patients when they were questioned about nusual feelings However no leading questions for pecific symptoms were asked

Systolic and diastolic blood pressure and pulse rate ere recorded during the stay in hospital and on the last ay of the treatment

Haemoglobin levels erythrocyte and leucocyte counts nal and hepatic function laboratory tests were also rformed

A possible influence on blood clotting was assessed in l three groups by the following tests

Thrombocyte count (3) Normotest (19) Ethanol gela on test indicating fibrinaemia (1?) Citrated plasma was ored at −20°C until immunoassay of antithrombin III At III) α_2 macroglobulin (α M) fibrinogen and lasminogen

Immunoassays were performed with the Mancini tech ique (18) Rabbit antiserum against At III was obtained om Nyegaard & Co Oslo Norway The other antisera ere obtained from Behringwerke Marburg/Lahn ermany Antifibrinogen serum was used for assay of DP In order to avoid coagulation the gel buffers ontained EDTA K 1 g/1 000 ml (10)

After conclusion of the treatment the follow up was udied with the help of a simple questionnaire which was anded to each patient This patient questionnaire had to sent back to the investigator after the first post partum enstruation Milk secretion as continuing lactation or a bound phenomenon spotting and/or the recommence ent of menstruation were recorded on the basis of pa nts replies

Statistical analyses concerning homogeneity of both groups were done by ?I Statistics or by U Test respective ly Mammary secretion mammary congestion uterine in volution general assessment coagulation test values be fore treatment spotting and rebound phenomena were evaluated by 2I Statistics only Blood pressure and pulse rate were analysed by both Wilcoxon Test and U Test The comparison between both groups with regard to dura tion of post partum amenorrhoea was performed by U Test

RESULTS AND COMMENTS

Prevention of mammary secretion (Table III)

Both preparations have shown an inhibitory effect on the onset of milk secretion During the last few days of the treatment there was a statistically significant difference in favour of CB 154 ($P<0\ 01$ on the 13th day) due to rebound in the DS group During the 10th to the 14th day of the study a postponed onset or continuation of lactation was observed in 8 of the 18 DS treated women In con trast to these findings milk secretion was seen in only 2 of the 20 CB 154 treated women during this period This difference is statistically significant on days 12 ($P<0\ 05$) and 13 ($P<0\ 01$) in favour of CB 154

Mammary congestion (Table IV)

This symptom occurred more frequently in the DS group than in the CB 154 group ($P<0\ 05$) due to rebound in the DS group Artificial emptying of the breasts was not necessary in any of the women

Table IV *Occurrence of mammary congestion*

oup		Treatment day		
		1st	7th	14th
3 154	Congestion/Total no of patients	0/20	1/?0 n s	0/20
	Congestion/Total no of patients	1/18	1/18	4/18

$=P<0\ 1$ $=P<0\ 05$ $=P<0\ 01$ $=P<0\ 001$

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LEUCINE AMINOPEPTIDASE ACTIVITY IN MATERNAL CORD BLOOD AND PLACENTA OF NORMAL PREGNANCY AND IN PRE ECLAMPSIA

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Abstract 1) Leucine aminopeptidase (LAP) was determined in maternal and fetal blood and in the placenta of mild and severe pre-eclamptic patients then compared to the levels of normal pregnancy 2) The enzyme activity increased significantly in severe pre eclampsia as compared with the mild type and with normal pregnancy 3) In mild pre-eclamptic patients LAP activity of maternal and cord blood did not increase significantly as compared with the normal cases but the placenta showed a slight decrease 4) The enzyme level in cord blood did not increase markedly in pre eclampsia

Leucine aminopeptidase (LAP) is a proteolytic enzyme needed in the terminal digestion of L leucyl peptides or the transfer of L leucine from one peptide mole to another It occurs principally in the small intestinal mucosa and in pancreatic extracts although it has been found in most human tissues animals plants and microorganisms The function of this enzyme in the blood is not known

Previous studies had clearly demonstrated that serum LAP activity increased during pregnancy (1 5 9) and that the serum level of this enzyme returns to normal 6–8 weeks post partum (1) reported increased serum LAP activity in normal pregnancy reaching the highest level during the last trimester and specifically at the time of delivery although the enzyme level in the cord blood was within normal limits

The substrate used for measuring LAP activity is hydrolysed by oxytocinase (3 10) and this accounts for the increased LAP activity in the serum of pregnant women It was shown that serum oxytocinase tends to decrease in pre eclampsia (6) (2) also demonstrated that decreasing levels of serum oxytocinase in severe toxaemia indicated diminishing placental function and impending fetal death On the other hand low level serum oxytocinase was demonstrated in patients with placental insufficiency (8) possibly due to impaired production or an excessive urinary leak of this enzyme The latter author also found that severe toxaemia was accompanied by a marked increase in the urinary excretion of leucine aminopeptidase although the urinary excretion of this enzyme remained relatively low throughout normal pregnancy as compared to normal non pregnant women

The purpose of this study is to measure the leucine aminopeptidase levels in maternal serum placenta and cord blood in pre eclamptic patients as compared with normal pregnancy and to assess its diagnostic value as a measure of placental function

MATERIAL AND METHODS

Thirty pregnant women were selected from the Maternity department of Ain Shams University Hospitals and they were classified into three groups (Table I) (*a*) 10 cases of normal uncomplicated pregnancy (*b*) 10 cases of mild pre-eclampsia (*c*) 10 cases of severe pre eclampsia

In this classification of mild and severe pre-eclampsia we followed the international standards of the Organisation Gestosis (7)

We collected the samples of maternal blood before the onset of labour while the placental and cord blood were taken immediately after labour All deliveries were vaginal with no complications and anaesthesia if needed was either local infiltration or pudendal block anaesthesia

Table I *The description of 10 normal pregnancies and 20 pre eclamptic patients submitted for enzyme estimations of the maternal and cord blood and placental tissues*

Type of cases	Age (y)	Parity	Gestosis index (G I)[a]
Normal pregnancy			
Mean	26 9	2 6	0 27
S D ±	5 7	2 8	1 03
Mild pre eclampsia			
Mean	27 1	2 30	3 80
S D ±	5 6	2 02	0 79
Severe pre eclampsia			
Mean	29 6	1 40	8 87
S D ±	8 99	2 17	1 85

G I is calculated by the sum of ratings of the edema proteinuria systolic and diastolic blood pressures

Blood samples were allowed to clot and the serum separated was kept at 4 for the enzyme assay within 24 hours

Placental samples were taken according to Ramadan et al (7) washed with ice cold distilled water then homogenized in distilled water for three minutes at a concentration of 1 mg/ml The homogenates were centrifuged at 2000 r p m for 5 minutes and the supernatant fluid was used for LAP assay

Aliquots of the maternal and cord blood sera and the supernatant fluid from the placental homogenate were used in duplicate for assaying LAP activity depending on hydrolysis of the substrate L-leucyl B naphthylamine hydrochloride where B naphthylamine will be freed and converted to a coloured azo dye by means of a diazotization reaction The colour density of the azo was assayed spectro-photometrically at 560 mμ according to method of Goldberg Pineda and Rutenburg (4) sults were expressed in mi rograms of B naphthylam liberated by 1 ml of a 2% dilution of the serum which is enzyme unit

RESULTS

Leucine aminopeptidase (LAP) activity showed significant increase in maternal and cord blood se and the placenta of severe pre-eclamptic cases compared with the corresponding values of mi pre eclamptic patients and with normal pregna women

The enzyme activity in mild pre-eclamptic p tients indicated a statistically not significant i crease in the maternal and cord blood sera as co pared with normal pregnant women but the place tal values from the first group were some than normal cases

The statistical analysis of LAP activity da carried out using Student s t test corresponding *P* value to indicate the si between each mild or severe pre ec normal pregnant women for maternal and blood sera and for the placenta All data ar resented in Table II

DISCUSSION

It has been reported that leucine aminopept enzyme is one of the changeable enzymes d pregnancy The general object of its study w see if any particular pattern of change is use

Table II *The estimation of leucine aminopeptidase enzyme in normal pregnancy and in pre eclamps*

Leucine aminopeptidase (LAP)	Maternal blood[a]			Cord blood[a]			Placenta[b]		
	Normal preg	Pre-eclampsia Mild	Pre-eclampsia Severe	Normal preg	Pre-eclampsia Mild	Pre-eclampsia Severe	Normal preg	Pre-eclamps Mild	Se
No of cases	10	10	10	10	10	10	10	10	10
Range	24–55	40–60	75–200	12–21	17–20	19–26	35–65	35–55	60-
Mean	42 0	49 0	107 0	17 1	18 5	21 8	51 0	49.2	6
S D ±	8 84	6 85	35 52	3 0	1 048	2 49	8 14	5 85	
Test of significance (*P*)	N S			N S			N S		
		$P<0\ 001$			$P<0\ 002$			$P<0\ 001$	
		$P<0\ 001$			$P<0\ 002$				

[a] LAP in terms of μg B-naphthylamine/ml
[b] LAP in terms of μg B naphthylamine/mg fresh tissue

he diagnosis of placental function in abnormal regnancy Our results indicated an elevated level f enzyme activity in the sera of normal pregnant omen before the onset of labour (mean 42 units) s compared with 10 8 units recorded by previous uthors as Mullan (8) for non pregnant women hereas LAP activity in the sera of the cord blood f the same cases was very low The enzyme activ y in the placenta of normal pregnancy was dis tinctly higher than that of the corresponding serum he hydrolysis of the substrate used for LAP activ ty by oxytocinase activity (3 10) may partially count for the increased results in normal pre nancy but this should not be taken into considera ion in placental insufficiency and in pre-eclamptic ases where the oxytocinase activity decreased in rum (2 6 9) Accordingly the results obtained in re eclamptic patients mainly represent the LAP tivity In severe pre eclampsia LAP activity had gnificantly increased in serum placenta and cord ood as compared with normal pregnancy and this nfirms the marked increase in its urinary excre n recorded by Mullan (9) Its high serum level ds to its spilling over in urine The elevation of P activity in mild pre eclamptic cases in serum d cord blood was not significant as compared th the normal group but the placenta showed a le decrease A sharp increase in LAP activity of h statistical significance was observed in mater l blood cord blood and placenta on comparing vere with mild pre eclamptic cases

The highly significant increase of LAP activity in maternal blood and placenta of severe pre amptic patients may be due to the degeneration d infarction of the placenta with release of the zyme in the maternal circulation Thus the centa can be considered as the main source of P enzyme in the maternal blood

The fetal blood level of LAP enzyme was not atly affected in pre eclampsia indicating that the zyme may not cross the placental barrier

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ON RADIATION DECREASED FIBRINOLYTIC ACTIVITY OF VESSEL WALLS

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stract Fibrinolytic activity was histochemically de rmined in biopsy specimens of the walls of human veins v epigastricae superficiales) obtained from 15 patients er irradiation of the lower abdomen because of malignant nital diseases and compared with non-irradiated con ols The activity was significantly lower ($p<0.001$) after diotherapy

e endothelium of certain vessels especially veins ntains activators of fibrinolysis which are liber d into the blood stream (6) These activators are portant for counteracting thrombosis (4) and in ue repair (1) They have also been studied in the lls of ovarian tumour vessels and have been con ered to be essential for growth of such lesions)

Malignant diseases treated with radiation are at ded by an increased frequency of thrombosis ich often starts in irradiated regions (8) Irradia n also alters tissue repair (9) Irradiation of a nour damages its vessels (11) and might help to ibit its growth —These effects of radiation may partly explained by damage to the vessel endo lial cells responsible for the production of inolytic activator enzymes

To check the validity of this assumption we died the histochemically determined fibrinolytic ivity in biopsy specimens of the walls of human sels in patients after radiotherapy and in non diated controls

MATERIAL AND METHODS

linical material consisted of 15 patients who had eived radiation treatment of the lower abdomen because arcinoma of the uterine body or cervix stages I–III

Venous biopsy specimens about 1 cm long were obtained from the left and the right superficial epigastric vein at operation via a Pfannenstiel incision The patients had received a total dose of 2000–4300 rad in this area

The interval between the end of radiotherapy and the operation was 5–13 weeks in 13 and 2½ years in 2 14 patients of comparable age who had been operated upon because of non-malignant conditions and who had not received medicinal or hormone therapy served as controls

The biopsy specimens were quickly frozen in rapidly expanding CO_2 to prevent freezing artefacts They were packed hermetically in Parafilm® to prevent dehydration and were stored at −60°C until examined

The *fibrinolytic activity* was measured with the histochemical method of Todd as modified and graded by Pandolfi et al (7) The vessels were cut on an International Harris cryostat in sections 8 μ thick and collected on pre-cleaned glass slides Four slides were prepared for each sample The sections on each slide were covered with 0 06 ml of fibrinogen (bovine fibrinogen essentially prepared according to Brakman (2) in concentration of 1% in phosphate buffer pH 7.8 ionic strength 0 15) and of 10 μl thrombin (Topostasin 70 NIH units ml unbuffered saline) The fibrinogen thrombin mixture was spread over an area of 10 mm² in order to obtain a fibrin film about 0 07 mm thick The slides were left at room temperature (21– 4°C) in a moist chamber for 30 minutes to stabilize the fibrin film One of the slides was immediately afterwards fixed in formalin while the remaining 3 slides were transferred to another moist chamber at 37°C and incubated for 10 20 30 minutes respectively after which they were fixed in formalin The fibrin slides and sections were stained with Harris haematoxylin Fibrinolysis was reflected by clear lytic areas in the fibrin film at the site of fibrinolytically active cells Three fairly distinct grades of fibrin digestion were recognized *grade I* microscopical punctate areas in most of the sections *grade II* gross lytic areas of irregular outline and sometimes confluent *grade III* dissolution of most or all the fibrin in contact with the sections A grade I slide was alotted 1 point a grade II slide 2 points and a grade III slide 3 points The total number of points scored by the set of 4 slides was taken as a measure of the fibrinolytic activity of the sample

Table I *Fibrinolytic activity of walls of irradiated and non irradiated superficial veins (median value and range in arbitrary units)*

Vein	Non irradiated	Irradiated
Superficial epigastric vein		
Left	8 (6–9 5)	3 (0 5–5 5) **
Right	8 25 (5 5–9 5)	3 5 (1 5–6)***

*** $p<0\ 001$

Comparisons between the fibrinolytic activity of different groups of veins were made by the *Wilcoxon rank sum test* (3)

RESULTS

The fibrinolytic activity of the specimens from the irradiated vessels was significantly lower ($p<0\ 001$) than in that of the controls (Table I) There was no significant correlation between the decrease in the fibrinolytic activity and the doses given But there was a tendency of the fibrinolytic activity to decrease with increasing interval between radiation and sampling (Fig 1) The two patients operated upon 2½ years after radiation still had low values (2 and 3 5 arbitrary units)

DISCUSSION

The results thus show that the fibrinolytic activity from irradiated vessels is significantly decreased compared with that of the controls We know from arlier observations in our laboratory that there is no significant difference in the fibrinolytic activity of

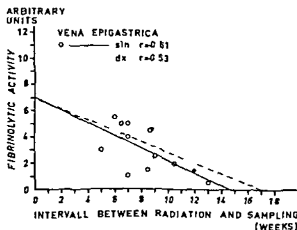


Fig 1 Comparison between fibrinolytic activity in superficial veins and interval between radiation and sampling

veins (superficial epigastric veins) from patients [...] cancer compared with those of healthy volu[...] (unpublished data)

In tissue culture studies it has been shown t[...] fibrinolytic activators are synthetized in the ve[...] wall probably in the endothelium (13) Irradi[...] directly damages the endothelial cells (11) it inhi[...] the nuclear DNA synthesis and effects the c[...] plasm mainly the structures which synthesize e[...] zymes (5) This helps to explain our finding o[...] significant reduction in the fibrinolytic activator c[...] tent of vessel walls after radiotherapy We did [...] find the reduction of the fibrinolytic activity to v[...] with the doses given There seems to be a corr[...] tion however between the reduction of t[...] fibrinolytic activity and the interval between rad[...] therapy and sampling (Fig 1) This is in agreem[...] with observations in animal experiments by [...] et al (12) and with the present finding of still l[...] values in the patients examined 2½ years after r[...] diation which suggests a permanent inhibiti[...] the synthesis of the activators The results m[...] help to explain such things as increased frequen[...] of thrombosis change in tissue repair and inh[...] tion of tumour growth in irradiated patients

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GROWTH OF THE FETAL SKULL WITH SPECIAL REFERENCE TO WEIGHT FOR DATES OF THE NEWBORN CHILD

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bstract Two growth curves of the fetal biparietal diame r are presented One is prospective based on the last enstrual period while the other is retrospective calcu ted from the date of birth The prospective curve shows slight decline in average values following the week 42 of station This is thought not to reflect a true shortening the biparietal diameter in the single fetus since serial easurements in single fetuses show growth up to the ne of delivery Individual growth curves grouped ac rding to the weight for-dates of the newborn child show trend towards longer biparietal diameters in the larger tuses Serial measurements preferably starting before ek 30 appear to be a good help in predicting birth ight but growth rates without regard to the actual asurement values were of little prognostic value in the esent material

veral curves of the normal growth of the fetal ull measured by pulsed ultrasound have been esented (4 5 6 8) These are similar in shape it they show parallel shifts along the metric axis iese differences are probably due to different apratus calibration Single measurements have been luable in the assessment of fetal age (5) Serial asurements have given more accurate informa n about fetal prognosis than urinary estriol asys (7) A previous report from our department owed a correlation between the fetal biparietal imeter and the weight for-dates of the newborn ild in a small series of pregnancies complicated pre-eclampsia (1)

We have now extended our observations and will sent normal curves for the biparietal diameter ed both on prospective and retrospective preg icy dating Furthermore in this new series we ll report the results of all individual cases of rmal and pre-eclamptic pregnancies in which or more measurements were performed classified according to the weight for-dates of the newborn child

MATERIAL AND METHODS

Normal pregnancies These were defined as single pregnancies in women with no pregnancy complications and live children without malformations These form the basis of the normal curves The material consists of 165 women with normal pregnancies

The prospective normal curve This was based on a definite dating of the last menstrual period in women with regular periods who did not take contraceptive pills shortly before the actual pregnancy irrespective of whether the pregnancy was terminated by induction or spontaneously Altogether 131 pregnancies fulfilled these criteria

The retrospective normal curve This was constructed retrospectively from the time of delivery in women who went into labour spontaneously Altogether 54 preg nancies fulfilled these criteria

Classification of the fetuses The fetuses were classified

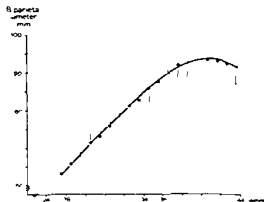


Fig 1 The smoothed normal prospective curve The actual figures are given in Table I

Table I *Weekly average values of the biparietal diameter in cases of normal pregnancy based on definite dating of the last menstrual period*

Gestational age (weeks)	No of observations	Mean (mm)	S D
24 5	3	70 7	5 5
25 5	1	63 0	0 0
26 5	5	65 6	5 3
27 5	13	71 6	5 4
28 5	13	71 3	6 2
?9 5	10	73 0	3 1
30 5	21	75 7	4 7
31 5	20	77 4	6 2
32 5	19	81 1	5 5
33 5	26	82 7	4 5
34 5	25	85 6	4 8
35 5	36	87 5	3 0
36 5	32	88 6	4 1
37 5	46	91 8	8 1
38 5	45	91 0	3 5
39 5	50	92 3	3 4
40 5	29	93 0	3 8
41 5	17	92 9	3 2
42 5	6	92 2	2 6
43 5	4	90 0	2 9

retrospectively in degrees of maturity according to standard tables of birth weight and gestational age (3) These tables were based on 1?5 485 births in Norway 1967 and 1968

(*a*) large for dates birth weight above 90th percentile
(*b*) medium-sized upper range birth weight between 50th–90th percentiles
(*c*) medium-sized lower range birth weight between 10th–50th percentiles
(*d*) small for dates birth weight below 10th percentile

The material comprises 22 children in group *a* 66 children in group *b* 88 children in group *c* and 16 children in group *d*

Measurements The biparietal diameter was measured by pulsed ultrasound using a diagnostic A and B scan unit made by Kretz Technik (series 4 100 MG) Before

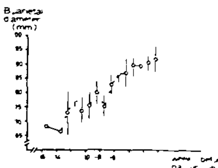


Fig 2 The retrospective normal curve The actual figures are given in Table II

Table II *Weekly average values of the bipa[...] diameter measured retrospectively from the t[...] spontaneous birth*

Week	No of observations	Mean (mm)	S D
0 5	39	92 3	4 7
1 5	29	90 9	3 0
2 5	20	89 8	3 2
3 5	14	89 9	4 ?
4 5	16	87 0	5 6
5 5	6	86 8	3 1
6 5	11	83 0	3 1
7 5	5	75 0	4 5
8 5	3	80 0	4 0
9 5	7	75 3	4 8
10 5	5	73 8	5 1
11 5	2	78 0	2 8
1? 5	5	7? 6	7 6
13 5	1	66 0	0 0
14 5	0	–	–
15 5	1	68 0	0 0

each measurement the apparatus was calibrated w[...] plexiglass cylinder which was constructed to give a [...] tance equivalent to 2 cm in tissue The velocity of [...] ultrasound beam was in the order of 1570 m/sec T[...] measurements were performed alternately by 3 exa[...] ers In a test series of duplicate measurements [...] standard deviation of the observer differences wa[...] mm (?)

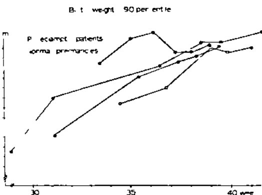
Statistical analysis The authors received help [...] recording and programming of the material for ele[...] data processing from the EDB section of the Medic[...] culty University of Bergen and are especially gra[...] programmer Alf M Aksland

RESULTS

The normal curves The prospective normal [...] is presented in Fig 1 and Table I The numb[...] observations after week 42 is small but there [...] indication of a decline in average values at this [...]

The retrospective normal curve is shown in F[...] and Table II This curve is less smooth tha[...] prospective curve The cause for this is prob[...] the smaller number of observations The retros[...] tive curve has a gradual increase up to the t[...] spontaneous delivery When delivery (time 0) [...] retrospective curve is set equal to 40 weeks [...] prospective curve the two curves are very si[...]

Individual growth curves The individual g[...] curves subgrouped according to the weight [...] newborn child are shown in Figs 3–6 Cases



3 Serial measurements of the biparietal diameter in uses who were large for dates at birth (above 90th centile)

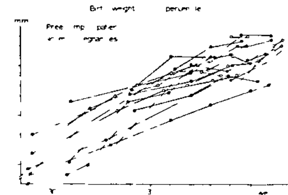


Fig 5 Serial measurements of the biparietal diameter in fetuses who were medium sized lower range at birth (between 10th–50th percentiles)

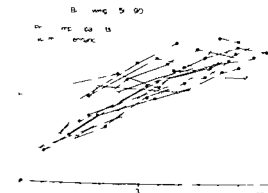
aternal pre eclampsia can be identified by open cles in the figures A comparison between the ures give the impression that there is a relation ip between the biparietal diameter and the birth ight of the newborn child However this appears be a statistical association rather than a clear-cut ognostic index in the single case This will be ther discussed below

Women with pre eclampsia had children in all th weight groups but their relative numbers in with decreasing birth weights of the ildren With a few exceptions the fetal skulls of -eclamptic mothers showed similar patterns to ose of mothers without pre eclampsia

The correlation coefficient between the biparietal ameter taken shortly before birth and the weight and length of the newborn child are shown in Table III

DISCUSSION

The shape of the prospective curve of biparietal diameter growth of the present investigation is simi lar to that presented by Willocks et al (8) with the exception of the slight decline following week 41 The differences in actual measurements between different normal curves is most likely to be due to calibration differences and not to reflect differ ences of fetal skulls The dip following week 41 is a phenomenon which is also seen in normal curves of birth weight (3) The present material is made up of serial measurements of the same individual and



4 Serial measurements of the biparietal diameter in ses who were medium sized upper range at birth ween 50th–90th percentiles)

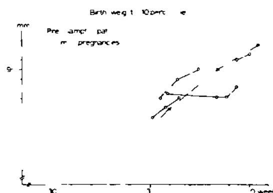


Fig 6 Serial measurements of the biparietal diameter in fetuses who were small for dates at birth (below 10th percentile)

Table III *Coefficients of correlation (r) between the biparietal diameter measured during the last week before birth and birth weight and length*

Condition	No of observa tions	Biparietal diameter versus birth weight (*r*)	Biparietal diameter versus birth length (*r*)
Normal pregnancies	58	0 58	0 72
Pre-eclamptic pregnancies	15	0 63	0 37

single measurements in other cases The single measurements were more frequent towards the end of pregnancy at which time several women were referred to the obstetrical department for evaluation of hypermaturity The shape of the curve is there fore thought not to reflect a true shortening of the biparietal diameter in individual fetuses It is more likely to reflect a biological phenomenon which means either a preponderance of small fetal skulls among those going past term or an incorrect preg nancy dating on the part of the mothers That the individual fetus does not show a shortening of the biparietal diameter is demonstrated in Figs 3–6 in which the trend of gradual growth up to the time of birth is evident The few instances of shortening of the biparietal diameters with time are thought to represent either observer s error (2) or pathological conditions in cases of pre eclampsia The re trospective curve using spontaneous labour as the int of reference eliminates the possible error of correct dating but may include some cases of premature labour

Individual growth curves grouped according to the weight for-dates of the newborn child should indicate whether it is possible to predict the size of child at birth Willocks et al (8) could predict the birth of a dysmature or a non dysmature child with a fair degree of accuracy using a growth rate of 0 17 cm per week as the dividing line We have not calculated the weekly growth indices but a glance at Figs 3–6 will show that such predictions would be of little value in these cases A comparison of the large (Fig 3) and the small (Fig 6) babies shows that the former as a rule had a slower growth rate from about week 30 onwards than the latter On the other hand the large babies had large biparietal diameters when first measured in contrast to the small ones Thus the general trend was a con vergence of the curves towards a normal aver with a smaller variation at term The two group medium sized babies show considerabl overl ping of the curves with a slight trend for the ba in the upper range to have larger biparietal diam ers The curves for fetuses of mothers with pr eclampsia show the same growth trends as thos mothers without disease with a few excep ns arrested growth not thought to be due to measur ment errors In a previous communication Berg & Brodtkorb (1) found a more marked correla between the biparietal diameter and pregnancy ou come than that of the present material Th fir included many women with severe pre-eclam who had severely growth retarded children wh the majority of the patients of the present m had mild pre-eclampsia

The correlation coefficients (Table III) se the impression that there is no strong associa between the biparietal diameter measureme is a the weight for-dates of the newborn child T nutritional status of the fetus affects the body t greater degree than it affects the head On the oth hand judged from the curves it seems that the ti of maximum growth rate of the fetal head may h prognostic significance Fetuses destined t large babies appear to have large biparietal diam ers before week 30 Therefore a measurement of biparietal diameter between week 20 and ... cases of known gestational age may prove to be best prognostic index of the size of the newbor child

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ALPHA FETOPROTEIN CONCENTRATION IN AMNIOTIC FLUID DURING THE LAST TRIMESTER IN NORMAL PREGNANCIES AND IN PREGNANCIES WITH SEVERE FETAL ABNORMALITIES

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stract The concentration of alpha fetoprotein (AFP) in amniotic fluid was studied during the last trimester of gnancy 1?9 samples of amniotic fluid were collected by nsabdominal amniocentesis in 94 pregnant women Only omen with uncomplicated pregnancies giving birth to rmal infants at term were included The 90% reference erval was calculated and a distinct decrease in the iniotic fluid AFP concentration was found during the last mester An AFP concentration above the 90% reference erval was found in 8 out of 10 cases of anencephaly ormal AFP concentration was found in a case of congeni heart disease with severe oedema and a low concentra n was found in a case of Down s syndrome (Trisomy 21)

reased alpha fetoprotein (AFP) concentrations in iniotic fluid in the last trimester have been re rted in neural tube defects in other severe lformations and in intrauterine fetal distress or onatal death (1 3 5 7 11 12 14) The normal P concentration in amniotic fluid in the last nester of pregnancy has not yet been clearly ined because of inadequate assay methods (1 3 because the samples were not all obtained by nsabdominal amniocentesis (1 3 11 12) and fi ly because normality was not uniformly defined The purpose of this study was primarily to esti te the 90% normal range for amniotic fluid AFP in last trimester of pregnancy in normal pregnant men by means of a sensitive AFP assay Sec lly the aim was to determine the AFP concen ion in amniotic fluid from pregnant women with ere abnormalities of the fetus

MATERIAL

mal specimens

transabdominal amniocentesis in 94 normal pregnant ien in the last trimester 1?9 amniotic fluid samples were obtained (≥3 punctures in 7 cases 2 punctures in 15 cases and 1 puncture in 72 cases) The punctures were performed between 9 and 12 in the morning Specimens contaminated with meconium (greenish) were discarded Only women with uncomplicated pregnancies and giving birth to normal infants of a birth weight ≥2 500 g at term (38–<42 gesta tional weeks) were included

Pathological specimens

12 amniotic fluid samples were collected by transabdomi nal amniocentesis (5 cases) and by rupture of the membranes (7 cases) from pregnant women with abnormal fetuses (see Table I)

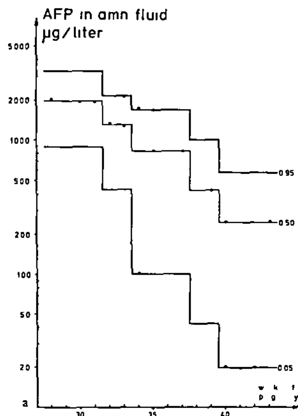
METHODS

The amniotic fluid samples were all centrifuged for 10 minutes at 1 500 g and the supernatants were kept frozen at −20°C until analyzed

Measurement of AFP

Quantitative radioimmunoelectrophoresis (RIEP) as re cently described (Nørgaard Pedersen 1974) (9) was used for determination of AFP in amniotic fluid

The RIEP gel plates were made by moulding a 1 5 mm thick gel between two gel plates The gel consisted of two parts the cathodic gel containing about 1 ng of ^{125}I AFP the anodic gel containing 0 03 (v/v) volume fraction of AFP antibody (Antibody Rabbit immunoglobulins against hu man α_1 fetoprotein Dakopatts Copenhagen) Just before use of the plates a row of wells was cut in the cathodic gel near the border of the antibody gel By means of a commer cially available primary standard (α fetoprotein standard 0 5 ml ??0 mg/l Behringwerke AG Marburg/Lahn) a secondary AFP standard containing 640 μg/l was prepared from a pool of amniotic fluids taken in the second half of pregnancy This standard was used in dilutions from 640 to 20 μg/l The wells were filled with exactly 15 μl of either samples or standards After high voltage electrophoresis for 4 h or low voltage electrophoresis for 18 h the gel plates were dried and submitted to autoradiography for ?4–48 hours using a common X ray film (Kodak® RP/L X Omat



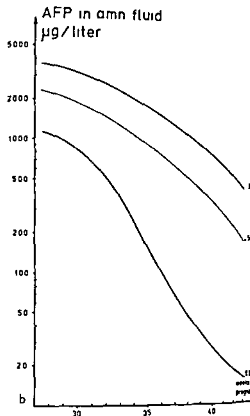


Fig 1 (a) The non parametric 90% reference curve for AFP in amniotic fluid from pregnant women in the last trimester of pregnancy (129 samples) *(b)* The corresponding smoothed curve for amniotic fluid AFP in the trimester of pregnancy

Table I *Amniotic fluid AFP concentration in 12 pregnancies with severe fetal abnormalities*

Transabdominal amniocentesis cases 1 3 7 9 and 11
Rupture of the membranes cases 2 4 5 6 8 10 and 12
H=high N=normal L=low

Case	Week	Newborn Sex	Newborn Diagnosis	Amniotic fluid AFP (ug/l)	
1	40	♀	Anencephaly	890	H
2	35	♀	Anencephaly	1 280	N
3	39	♀	Anencephaly	147 000	H
4	36	♂	Anencephaly	79 150	H
5	29	♂	Acrania	53 500	H
6	34	♀	Acrania	8 900	H
7	33	♀	Anencephaly	20 700	H
8	35	♀	Anencephaly	700	N
9	40	♂	Anencephaly	15 200	H
10	39	♀	Anencephaly	2 270	H
11	36	♂	Anasarca m gr morbus cordis	1 300	N
12	40	♀	Down s syndrome	20	L

Intrauterine death of the fetus The samples were collected before fetal death

Medical X ray film) in order to localize the rockets B of an LKB RCC 2105 spark chamber it was obtain a polaroid picture of the rockets within 10-3 nutes (17) The analytical coefficient of variation was lated on the basis of 20 determinations on a pool of am fluid samples with an AFP concentration of 380 μg/ was found to be 10 2% The sensitivity of t 20 μg/l Using this method one technician can perform 40 AFP measurements in duplicate

Statistical method

A non parametric method was used for the computat gestational age dependent reference intervals of (Winkel & Jørgensen 1973) This method repeated bines data of consecutive age groups A program was used for the computation of the re intervals At each step gestational weeks with a difference between the location of the quantity tions are combined provided that the location dispersions do not differ significantly with regard specified levels The specified significance level study was 0 10 corresponding to a *P* value of 0 05 F reference intervals were computed for the resulting tional groups

RESULTS

mniotic fluid AFP levels during e last trimester of pregnancy

he 90 % tolerance interval for amniotic AFP during e last trimester of pregnancy is shown in Fig 1 A g 1B represents the corresponding smoothed urve This curve was made by drawing the best ting smooth curve to Fig 1 A A gradual decline in AFP concentration was found from the 27th to 40th week of gestation

nniotic fluid AFP levels from pregnant men with abnormal fetuses

all cases of anencephaly except cases 2 and 8 nificantly elevated AFP concentrations were ind whereas a normal concentration was ob ved in a case of congenital heart disease with vere oedema and a low concentration in a case of wn s syndrome (Trisomy 21) (Fig 2)

DISCUSSION

om the computed non parametric curves in Fig and the smooth curves in Fig 1B it is seen that normal range for AFP in amniotic fluid is rather le and that a steady decrease is seen from the 27th he 40th gestational week The AFP concentration mniotic fluid in this period is considerably lower n during the first half of pregnancy (9) A com ison between the present results and the results in r studies is difficult mainly due to differences in sampling procedure (puncture or rupture of the nbranes immediately prior to delivery vaginal niocentesis puncture of the membranes during sarean section or transabdominal amnio- tesis) differences in assay technique and in nition of normality and finally because of the of different AFP standards (1 3 5 7 11 12 15)

in the present study all 129 specimens were ined by transabdominal amniocentesis in 94 mal pregnant women all giving birth to normal nts The general pattern for the AFP concentra in amniotic fluid in the last trimester of preg y as seen in Fig 1 is similar to the pattern ribed by others (1 3 7 11 13) However the concentrations in relation to gestational age is e than twice as high as reported by Seppala & slahti (12 14) and considerably lower than found Brock & Sutcliffe (3) The reason for these dis

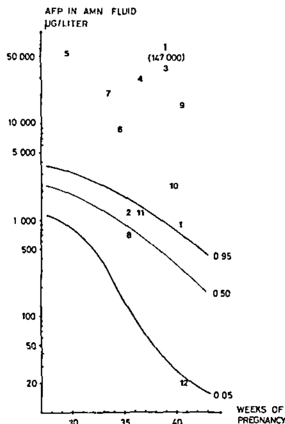


Fig 2 AFP concentration in amniotic fluid from pregnant women with abnormal fetuses The reference curves cor respond to Fig 1 A

crepancies may be explained mainly by differences in standardization (14) and measurement Seppala & Ruoslahti have found the Behringwerke standard about twice as high as their own standard (12 14) AFP quantitation methods with a sensitivity of 20 µg/l or lower must be used for determining the normal AFP concentration in amniotic fluid in the second half of pregnancy However AFP assays with a sensitivity of about 200 µg/l (8) may be used to show whether the AFP concentration is above or within the normal range This is important because these rather insensitive measurements usually can be finished within a few hours From our measure ments of AFP in amniotic fluid no close correlation has been found between the AFP concentration and gestational age as found by Seppala & Rouslahti (14) However AFP concentrations below 100 µg/l indicate that the pregnancy has advanced to at least the 33rd gestational week (see Fig 1 A) The AFP concentrations found in amniotic fluid from pregnant women with abnormalities of the fetus are in agree

ment with the findings in similar studies (1 3 5 7 11 12) *The normal AFP concentration in amniotic* fluid in 2 out of 10 cases of anencephaly do not exclude an elevated AFP concentration in the early pregnancy period in these two cases (cases 2 and 8) As shown in several studies it is especially during the first half of pregnancy that increased AFP concentrations in amniotic fluid is of practical importance (1 3 5 6 7) During the second half of pregnancy AFP measurements have especially been used to *monitor severe Rhesus isoimmunisation and in the* diagnosis of intrauterine fetal distress or death (11 12 13 15) Also in other types of fetal malformation than neural tube defects elevated AFP values have been found (11) It should be emphasized that *amniotic fluid samples from Rhesus isoimmunisa*tion patients could not be used for calculation of the 90% reference interval since increased AFP concentrations have been found in these patients (2 13 15) The diagnostic significance of AFP measurements in amniotic fluid in the second half of pregnancy has not yet been clearly defined Similar measurements in maternal serum may be simpler and perhaps more acceptable in clinical *practice*

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THE VALUE OF AMNIOTIC FLUID DIAMINE OXIDASE ESTIMATIONS IN THE MANAGEMENT OF SEVERE RHESUS ISO IMMUNIZATION

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act Serial estimations of the enzyme diamine ox (D A O) in liquor amnii were made in 87 rhesus ised women Normal levels were found in severe se with a favourable fetal outcome but abnormal s were found in 50% of the pregnancies in which e disease was associated with fetal death In addi when liquor bilirubin levels predicted moderate se disease D A O levels were abnormal in 75% of the iancies in which the fetus succumbed Abnormally D A O levels in amniotic fluid were frequently as ted with the subsequent development of dissemi l intra vascular coagulation in the infant Serial esti ons of D A O in amniotic fluid could be a helpful ct to serial liquor bilirubin estimations in the man ent of severe rhesus iso-immunisation

ough perinatal deaths due to rhesus iso-unisation continue to decrease in this country e remains the need to improve the prognostic lity of pre natal investigation in detecting not the severely affected fetus but those which survive with skilled obstetric and paediatric

stimation of the bilirubin concentration in liquor ii is the recognised method of predicting the erity of the condition in the fetus

However interpretation of the results may mis esent the severity of the effects of the disease he fetus leading to inappropriate management of individual cases (6) Errors may also be due to technical difficulties (2) or inaccurate estimation of gestational age Additional guidelines would help to eliminate these errors

In an earlier report (9) we concluded that serial estimation of the enzyme in amniotic fluid might provide an indicator to the ultimate fetal outcome

In this larger study the results of 331 D A O estimations in amniotic fluid from 95 women 82 of whom had rhesus iso-immunisation are presented

PATIENTS AND METHODS

In patients with suspected rhesus iso-immunisation amniocentesis was performed on one or more occasions between 22 and 37 weeks gestation after ultrasound placental localisation Five millilitres of maternal blood was taken at the same time In addition fetal ascitic fluid was obtained at the time of intra-uterine transfusion on 35 occasions D A O was measured using the method of Okuyama & Kobayashi (5) with modifications described by Southren (7) In order to provide a rapid method of estimation further modifications were made

To increase the sensitivity the Carbon 14 was doubled and neat liquor samples were used (Normally a 1 in 10 dilution is employed) The incubation time was also reduced to 15 minutes and separation of aqueous layers was effected by standing for 5 minutes at room temperature before pipetting off the upper solvent layer for counting

The D A O concentration in the serum and amniotic

ole I *The mean values of amniotic fluid diamine oxidase in pregnancy after 25 weeks gestation iplicated by rhesus iso-immunisation and in unaffected pregnancy*

erity of rhesus immunisation	No of patients	No of estimations	Geometric mean (mU/l)	Actual range
ffected	13	36	4 763	1 076–13 990
l	17	47	5 034	486–18 681
lerate	17	67	6 671	2 009–17 270

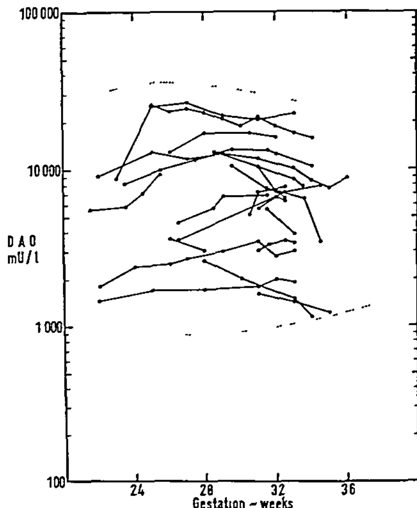


Fig 1 D A.O levels in amniotic fluid in 21 pregnancies of rhesus iso-immunisation in which the baby survived (? estimations) The dotted lines indicate the normal range limits

fluid was expressed in mU/litres (8) The bilirubin content (ΔOD 450) of the amniotic fluid was estimated by the method described previously (2)

The 95 cases were classified by severity of rhesus iso-immunisation into the following four groups

(*a*) 13 unaffected infants—Coombs test result negative (36 estimations)

(*b*) 17 infants with mild disease—Coombs test result positive but exchange transfusion not needed (? estimations)

(*c*) 17 infants with moderate disease—Coombs test result positive and exchange transfusion required, criteria for severe disease not satisfied (67 estimations) and

(*d*) 48 infants with severe disease (181 estimations), ? of whom were delivered alive with a cord haemoglobin less than 9 g/100 ml or a cord bilirubin of over 7 mg ? and 16 of whom were stillborn

Of the 32 infants alive at delivery in this last group eleven died during the neo-natal period

Table II *Geometric mean of liquor diamine oxidase mU/l with 95 % limits (t 0 05×S D)*

Unaffected (13 cases) mild (17 cases) and moderate (17 cases) (Includes only one point per patient per gestational group)

Gestation (weeks)	*n*	Geometric mean (mU/l)	95 % limits
22–25	9	6 243	1 136–34 301
26–29	17	5 702	914–35 563
30–33	39	5 211	1 010–26 871
34–37	36	5 123	1 235–21 251

RESULTS

Amniotic fluid

The geometric mean levels of D A O in amniotic fluid after 25 weeks gestation taken from unaffected pregnancies and those complicated by mild and moderate disease is shown in Table I.

In 2 cases of mild disease D A O levels in liquor amnii were consistently under 1000 mU

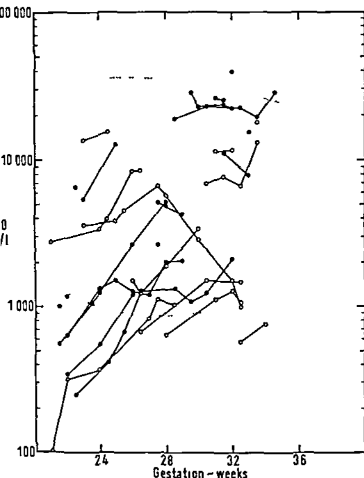


Fig 2 D A O levels in amniotic fluid in 27 pregnancies (11 N N D and 16 S B) in which the fetus succumbed (88 estimations)

om earlier studies we know that the D A O levels amniotic fluid are reasonably constant in the last nester (9)

Since statistically no significant differences re found between levels in unaffected preg ncies and those from pregnancies complicated mild and moderate rhesus disease the 150 estu tions were grouped together

The upper and lower 95% limits (t 0 05× S D) for s combined group at various gestational periods given in Table II Thus has been used as the rmal range

The 48 severely affected pregnancies were con ered according to fetal outcome In 21 patients estimations) in whom the fetal outcome was ourable there were no D A O levels in the am tic fluid outside our normal range (Fig 1)

The remaining 27 pregnancies (88 estimations) ded in either intra-uterine death (I U D)—16 gnancies or neonatal death (N N D)—11 pregnancies In 21 of these pregnancies in which serial D A O estimations were available 50% had one or more D A O levels outside the normal range (Fig 2) In the remaining 7 pregnancies 3 or 43% of single estimates of D A O were outside the normal range

Using a University College Hospital modification of the Liley type prediction chart based on liquor ΔOD 450 (ΔOD 450 at 24 weeks<0 3 at 28 weeks

Table III *Summary of D A O levels and fetal outcome in pregnancies complicated by severe and moderate–severe rhesus iso-immunisation*

Liley ΔOD 450 prediction zone	Total no of cases	No of SB/NND	No of SB/NND with abnormal D A O levels
Severe	25	19	7 (37%)
Moderate–severe	2_	8	6 (75%)

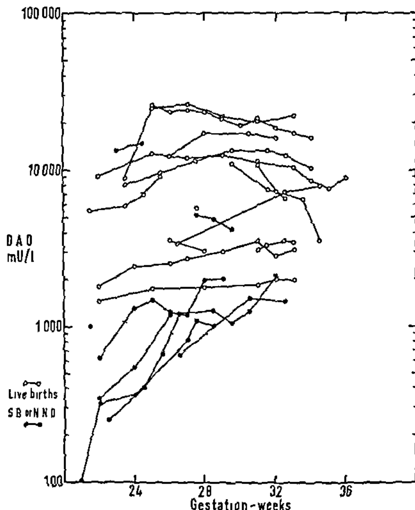


Fig 3 D A O levels in a[mniotic] fluid in 22 pregnancies pr[edicted] in moderate–severe range

<0 22 at 32 weeks<0 17 Fairweather et al (3)) 25 pregnancies were predicted as having severe disease Seven (37%) of the 19 pregnancies in this group that ended in perinatal death had abnormal D A O levels in the amniotic fluid In some of these cases abnormally high levels were found However of those predicted as moderate to severe there were 8 cases in which perinatal death occurred In 6 of these (75 %) the D A O levels in amniotic fluid were abnormally low (Table III and Fig 3)

One severely affected baby had bilirubin values predicting mild disease or an unaffected pregnancy and a favourable outcome associated with normal D A O levels

Of the severe cases studied 15 had one or more intra uterine transfusions No significant difference ($p<0\ 7$) was found between the levels of D A O estimated before and after one or more transfusions

Abnormally low liquor D A O levels (below 95% lower limit) were associated with 5 of 6 bab[ies in] which disseminated intravascular clotting (D[IC]) was diagnosed prior to N N D The levels [in the] sixth case were also low falling just with[in the] lower 95% limit

In 5 cases of N N D where D I C wa[s not] diagnosed despite routine neonatal scre[ening] D A O levels were within normal limits

There were two surviving babies in which [DIC] was diagnosed Liquor D A O levels in on[e] were bordering on the lower 95% limit wh[ile the] clotting defect in the other was mild and w[as as]sociated with normal D A O liquor levels

Amniotic fluid/serum D A O ratio

The ratio was investigated in the different cla[sses of] rhesus disease after 28 weeks when the ra[tio would] be expected to be constant (9) The mean [and] the ratio in each group are shown in Table [IV] When the mean ratio of the unaffected gro[up]

able IV *Amniotic fluid/serum*
iamine oxidase ratio after 28 weeks gestation
rithmetic mean ±1 S D

	No of cases	No of estimations	Arithmetic mean	S D
naffected	9	18	2 53	±1 46
ild	15	37	3 21	±1 77
oderate	16	50	4 80	±4 28
vere	35	98	5 07	±3 09

ompared with the mean ratios of the moderate and vere groups a statistically significant difference as present ($p<0\ 05$ and $p<0\ 001$ respectively) imilar findings were present when the mean ratio the mild group was compared with the mean itios of the moderate and severe groups

However no significant differences were found tween unaffected and mild groups or between oderate and severe groups

Ascitic fluid

A O was estimated in 35 samples of fetal ascitic uid obtained at intra uterine transfusion The ean level was 33 mU/litre (range 0-123 mU/L) A omparison of D A O levels in amniotic fluid and tal ascitic fluid taken from the same patient iowed a statistical difference ($t=4\ 8997$ $p<0\ 001$ =35)

DISCUSSION

conventional tests of feto-placental function r little guidance to the clinician in the manage nt of severe rhesus iso-immunisation Endocrine s including the determination of maternal uri y oestriol pregnanediol and chorionic gonado- phin are of scant value (1) although the estima 1 of placental lactogen (10) may provide an indi ion of fetal outcome

There is little difficulty in detecting the very se ely affected fetus using serial liquor analysis for rubin but the perinatal mortality is high despite ert obstetric and neonatal management

In this group abnormal D A O levels in the liquor re only found with an unfavourable outcome wever a normal level would not preclude a sub- quent perinatal death

There was a surprisingly high perinatal mortality e (36%) in the pregnancies in which moderate–severe disease was predicted Salvage of these babies is likely to be the most rewarding and serial estimations of D A O in the liquor would be of considerable value Abnormally low levels were found in 75% of the pregnancies with perinatal deaths

We were unable to confirm our earlier finding (9) that amniotic fluid/serum D A O ratio correlated with the ΔOD 450 Although the ratio increased with aggravation of the disease the scatter in the values of the ratio did not always reflect the fetal condition in individual cases

It is of interest that liquor D A O levels did not appear to be affected by intra uterine transfusion suggesting that the procedure has an insignificant effect on the underlying disease process

We are unable to offer an explanation for the association between low D A O levels in the liquor and the subsequent onset of disseminated intra vascular clotting (D I C) in the baby Not only did 83% of the N N D with D I C have levels below the 95% lower limit but the D A O levels in liquor in 2 out of the remaining 3 cases with D I C had levels bordering on the lower 95% limit

Is the detection of D A O in amniotic fluid of any value to the clinician?

Although the estimation of the liquor D A O does not necessarily detect the cases with severe disease with an unfavourable outcome normal D A O levels when severe disease is predicted would encourage the clinician to undertake intra uterine transfusion in circumstances in which active management may be considered hopeless We like others (4) have found difficulty in diagnosing the degree of hydrops and anaemia in the fetus in utero an assessment which influences the timing of the initial intra uterine transfusion

In the moderate–severe group the finding of abnormally low liquor D A O levels would alert the clinician to the probably poor fetal outcome Similarly monitoring the coagulation factors in the new born prophylactically in these cases may significantly reduce the perinatal mortality

We have also found that the rapid method for estimation of D A O can be used to distinguish liquor amnii from ascitic fluid Blood staining of the fluid can make their differentiation otherwise difficult

In conclusion we suggest that by using the simplified method for the estimation of D A O the measurement of serial levels of the enzyme in the

liquor routinely obtained for bilirubin analysis could make a considerable contribution to the planning of the pre natal and neonatal management of severe rhesus iso immunisation

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CASE REPORTS

EXTRAMEMBRANOUS PREGNANCY WITH AMNIORRHOEA

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stract A case of extramembranous pregnancy is re ted From about the 10th week of pregnancy there was intermittent loss of liquor amnii which from about 25th week became continuous The infant was born ve in the 31st week but died 15 days later because of respiratory distress syndrome The placenta was cumvallate with short thick membranes unable to ver more than a small part of the infant The course of pregnancy and the prognosis of the infant are dis ssed on the base of previous publi ations Because of poor prognosis for the infant it is suggested that in ruption of the pregnancy should be considered in early es of amniorrhoea

mature rupture of the membranes with continua n of the pregnancy and retraction of the mbranes after which the fetus develops partly tside the membranous sac has been known since beginning of this century when Meyer Ruegg collected publications of 14 separate cases In ent years several single cases have been re ted (2 4 6 10 11 12 13)

These cases are rare but of interest because of the blems arising

CASE REPORT

patient was a 27 year-old gravida 2 who 2 years viously had had a normal pregnancy She had a regu nenstrual cycle and her last period began on June 3 I After 10 weeks of amenorrhoea she was admitted to pital because of brown vaginal di charge for 3 weeks a loss of clear fluid vaginally for ? days The uterus enlarged as expected and the cervix was normal ing an 11-day stay in hospital no loss of fluid was rved and the patient was discharged

uring the following ? months the patient several times rved a loss of clear fluid vaginally but examinations wed that the size of the uterus was compatible with the od of amenorrhoea and the cervix was closed

t 25 weeks gestation the pat ent was readmitted to pital with a continuous loss of clear fluid vaginally which continued until delivery The fluid was examined for bacterial growth and α hemolytic streptococcus sensitive to penicillin were found Penicillin (Vepicombin®) was given without interruption until delivery Once a week the fluid was examined bacteriologically and Gram negative rods—like Klebsiella—were found They showed only slight sensitivity to a few antibiotics and specifi antibiotic treatment was therefore omitted

The genital region was kept as sterile as possible and no clinical signs of infection occurred

The growth of the uterus continued normally and the values of urinary oestriol were rising

By means of a Tassaway® rubber-cup the amount of vaginal fluid was estimated to be a maximum of ?00 ml a day The content of protein in the fluid was 3 9% which indicated that the fluid was a combination of liquor amnii (protein content 0 ?%) and plasma (protein content 7%) The serum protein content of the patient was 7 0%

At 31 weeks gestation (on January 5 197?) spontaneous labour supervened with a breech presentation A live female child weighing ?050 g was delivered Because of its low weight the child was immediately transferred to the pediatric department

The placenta weighed 680 g The membranes were short and thick with slight thickening of the free margin and fibrin at the base The cord contained 3 vessels and there were no signs of infarction The placenta was circumvallate (Fig 1)



Fig 1 The circumvallate placenta showing the short membranes with the thickened edge

Table I *Data concerning rupture of the membranes duration of pregnancy and birth weight publish the recent years*

Author and year of publication	Duration of pregnancy at membrane rupture (weeks)	Duration of amniorrhoea (weeks)	Duration of pregnancy (weeks) at delivery	Birth weight (gram)
Erskine 1945 (4)	18	17	35	2 000
Siddall 1946 (13)	18	13	31	1 950
Nold 1957 (10)	21	14	35	2 080
Rosset 1957 (12)	23	9	32	1 450
Carpenter 1965 (2)	20	15	35	1 950
Ringe 1967 (11)	23	7	30	1 400
Kohler & al 1970 (6)	16	11	27	1 100
Present case	11	20	31	2 050

The puerperium was uneventful The treatment with penicillin was stopped at delivery

Shortly after birth the child showed signs of the re *spiratory distress syndrome It was treated with antibiot* ics and because of rise in the bilirubin values exchange transfusion was performed Death occurred at the age of 15 days Growth of *Klebsiella pneumoniae* was found at the time of death in the trachea and in the blood Autopsy was not performed but no external malformation was seen

DISCUSSION AND CONCLUSION

The intermittent loss of liquor amnii at the beginning of the pregnancy may be explained by a regeneration of the membranes which has been shown ... imentally to occur in the guinea pig (14)

At the first admission to hospital there was doubt whether the fluid was liquor amnii or not Examination with Nile blue sulphate is not helpful until after the 30th week of pregnancy (7) but when the fluid occurred in an amount large enough to collect estimation of the protein content suggested that it was a mixture of liquor amnii and plasma

Most of the published cases of this kind are single cases Table I shows some recent publications It is seen that loss of liquor amnii in most cases occurred in the middle of the second trimester and premature delivery occurred in the middle of the third trimester All the infants were alive at birth but died within a few hours except in the case described by Carpenter (2) This child survived and showed at the age of 17 months only slight retardation The infant in our case survived for 15 days

Two of the infants mentioned in Table I were malformed and in one child congenital luxation of the hip was found Amnionitis occurred only in the case described by Ringe (11) However prema rupture of the membranes does increase the ri amnionitis and sepsis which increases with length of the amniorrhoea (1 3 5)

Both a reduced (1) and an unaltered (8) peri mortality have been described after using a biotics in cases of premature rupture of membranes To avoid infection it may be portant to keep the genital region sterile

As even symptomless cases of amnionitis cause sepsis in the child in the neonatal period the infection with *Klebsiella pneumoniae* w was found before the death of the infant may come from the Klebsiella like infection of mother The long interval (2 weeks) during the child was treated with antibiotics how speaks against this The placenta was circu late which is a common finding in these cases

The poor prognosis for the child the risk of tion and the emotional strain of a protracted s hospital are factors which may tempt the obs cian to induce labour Improved prophyla treatment for infections and improved ma ment of the premature baby may howeve prove the prognosis for the child but interr of the pregnancy may be considered in early of amniorrhoea

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TRISOMY D IN A CYCLOPS WITH CARDIOVASCULAR DEFECTS

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stract A case report of cyclops with trisomy D in a nale infant associated with cardiovascular defects is sented A survey of the literature pertaining to other ported cases of cyclopia is presented to establish the obability of the existence of at least two distinct ologic groups of cyclopia—those associated with somy D and those associated with other chromoso-l aberrations single gene mutations or non genetic tors

ie term arrhinencephaly described a wide group facio-cerebral malformations cyclopia being considered the most severe anomaly of this type (12) This has recently been reclassified as a specific type of alobar holoprosencephaly (5)

Cyclopian malformation is characterized by a single central orbital cavity and a nose like tubular appendix situated above the orbit (19) To the best of our knowledge only 16 cases of cyclopia have been reported in which chromosomal studies had been performed (Table I)

In only four of these cases a normal karyotype was reported while among the others four distinct

ble I *Karyotypes and extracephalic defects in cyclops*

thor	Karyotypes	Extracephalic and extrafacial malformations
ıkaki & Waxman (1)	47XX D+	Abnormal anal opening position (autopsy not done)
ts et al (?)	47XY D+	Polycystic kidneys persistent omphalomesenteric duct splenomegaly persistent thyroid pyramidal lobe cryptorchidism with hypoplastic testes abnormally thick scalp and polydactyly
non et al (3)	47XX D+	Diaphragmatic hernia dextrocardia hepatosplenomegaly and hyperflexion of fingers
ıen (4)	46XY/45XY G−	Renal anomalies bilateral hydroureter trigger thumb and short neck
ıt & Lewis (6)	46XX 18p−	Hypoplastic adrenal and thyroid
ob et al (7)	47XX D+	Polydactyly
lin & Cohen (8)	Normal	No information
ɔrecht et al (9)	47XX D+	None
nden et al (10)	Normal	No information
rg (11)	Normal	No information
ᵛune et al (13)	Normal	No information
wsky et al (14)	46XX 18p−	None
ıppe et al (15)	47XX D+	Polydactyly
er (16)	46XY/47 ext min +	No information
ıı & Tinaztepe (17)	47XY D+	Patent ductus arteriosus atrial septal defect dextrocardia coarctation of aorta malrotation of intestines Potter type III polycystic kidney ectopic splenic tissue and polydactyly
ws & Jones (18)	47XX D+	Ovarian agenesis and hyperflexion of fingers
ent case	47XX D+	High interventricular septal defect hypoplastic pulmonary artery transposition of great vessels and hyperflexion of fingers

anomalous karyotypes have been described (Table I) Trisomy D has been found in eight of these cases two of which were associated with cardio vascular defects (17 3)

In this report we present an additional case of trisomy D in a cyclops with cardiovascular defects

CASE REPORT

The infant was born to a 41 year-old white American woman after a gestation of 36 weeks Three previous pregnancies resulted in a macerated fetus and two normal children (one male and one female) In the present preg nancy toxemia and hydramnios were noted during the last month of pregnancy prior to delivery There was no history of familial congenital malformations parental con sanguinity or X ray exposure Drug ingestion was limited to the last month of pregnancy for the treatment of the toxemia No other drug therapy was reported during pregnancy

The propositus was born by spontaneous delivery after a short labor Physical examination at birth revealed a female infant weighing 1800 g and measuring 46½ cm in length with an Apgar Score of 5 The baby showed the

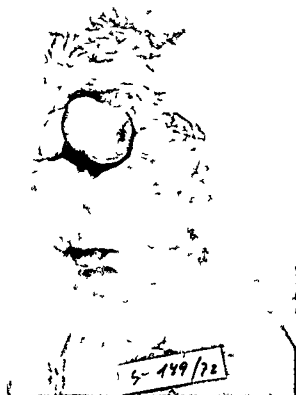


Fig 1 Close up of face showing the characteristic features of cyclopian malformation

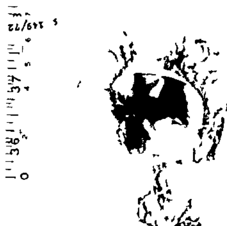


Fig 2 Coronal section of brain showing a single ventr with no signs of separation

characteristic features of cyclopian malformation a c central orbital cavity with a rudimentary palpebral fis on either side Above the orbit a tubular appendix wi blind opening resembling a nose was found (Fig Hyperflexion of fingers was observed as well

The infant died 55 minutes after delivery

PATHOLOGY

Upon post mortem examination defects were covered in only two organ systems the ce nervous system and the cardiovascular system amination of the C N S revealed a brain one the normal weight for its age (83 g cf 355 g nor ly) Brain dimensions were also small 6 cm le cm wide and 4 cm high The two cer hemispheres were fused and formed a single —except for a delineation in the posterior-occ region (for a length of 2 5 cm) The gyri were tened and the outer surface of the brain sh marked congestion

Upon examination of the base of the brain olfactory bulbs optic nerves and optic ch were found to be absent Coronal section of cerebrum revealed a single ventricle with no s of separation (Fig 2) The inner surface of th tricle was smooth and glistening The corpus losum and septum pellucidum were not to be f The brain tissue surrounding the single ve was 0 8–1 2 cm wide and there was no clear se tion between grey and white matter The pos caudal part of the aqueduct the cerebellu fourth ventricle and the medulla oblonga normal



Fig 3 Karyotype from cultured blood showing trisomy D (The Sheba Medical Center Cytogenetics Laboratory Tel Hashomer)

The cardiovascular system defects included high ventricular septal defect hypoplastic pulmo-y artery and transposition of the great vessels

CYTOGENETIC STUDIES

mediately upon death a blood sample via trans diac puncture was taken for chromosomal alysis The resulting leucocyte cultures revealed hromosome count of 47 in all 30 cells of the ture The additional chromosome was of the D-group The sex chromosomes were XX This is a variant of trisomy D 47,XX D+ (Fig 3)

DISCUSSION

Of the various karyotypes associated with cyclopia (Table I) trisomy D has been described with the greatest frequency and this form of cyclopia is the only one which is probably of the type of facio cerebral malformations described by Kundrat (12) as arrhinencephaly This evidence strongly sug gests the possibility of classifying this malformation

into two distinct causal groups In one group the causative factor may be chromosomal abberrations other than trisomy D or in the case of normal karyotypes some unknown entity In the other group trisomy D is the causative agent In our case this theory is supported by the cardiovascular findings which are characteristic even in non cyclopic cases of trisomy D

It has been accepted that extracephalic malformations are present in arrhinencephaly with trisomy D In all but one of the reported cases of cyclopia with trisomy D extracephalic malformations have been found This report by Halbrecht et al (9) seems to question the validity of the above classification by describing a case without such findings

The extracephalic malformations described in cyclopia associated with trisomy D show no uniform pattern however polydactyly also a typical finding in non cyclopic trisomy D has been described in 4 out of 8 cases (Table I)

In conclusion it is our conviction that arrhinencephaly with trisomy D and cyclopia with trisomy D are related entities with trisomy D being the common etiologic factor The second group including cases of cyclops either associated with normal karyotypes (etiologic factors of which remain to be discovered) or with chromosomal aberrations not of the D group most probably belong to different types of facio cerebral malformations

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OPEN RUPTURE OF THE SYMPHYSIS PUBIS DURING SPONTANEOUS DELIVERY

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clinical and roentgenological picture of phy siolysis is very well known In contrast the r syndrome of the rupture of the symphysis is during spontaneous delivery is less well wn

/e herewith report a case of rupture of the iphysis pubis during spontaneous delivery

CASE REPORT

year-old woman para 1 gravida 1 was admitted to the etric Ward on the 27th of June 1973 at the beginning bour Her pregnancy had been normal

x hours after admission she was delivered of a boy hing 3850 g A right medio-lateral episiotomy had performed before delivery After the delivery of placenta the patient complained of a sharp pain in egion of the symphysis At examination a rupture e vagina was found The rupture started above the ra The bladder and the urethra were drawn into agina. Through the rupture the pubis bone were seen an interval of 3 5 cm between them Between the s ruptured periost was seen (Fig 1 2)

e ruptured vagina was sutured with the replace of the urethra and the bladder The orthopaedic nent of the ruptured symphysis was a fixation of the c bones aided by tight pelvic binder during 3 weeks ley catheter was inserted into the bladder for 12 days patient received also antibiotic and analgetic therapy ree weeks after complete bed rest she had still ng difficulties and pains in the retropubic area An of the pelvis showed the almost complete disappnce of the rupture

ee months after the rupture she had completely ered (Fig 3)

DISCUSSION

iterature discussing separation or rupture of ymphysis pubis during spontaneous delivery is very scarce The opinions about the frequency of this phenomenon are divided Cibils (2) cites Boland (1934) who found a frequency of 1 rupture to 521 deliveries and Eastman (1966) who found a frequency of 1 rupture to 20 000 deliveries

The etiology of the rupture is not very well



Fig 1



Fig 2

known yet As is well known progesterone and relaxine heighten the degree of elasticity of the ligaments of the pubis bone According to Trillat et al (3) the limit of elasticity during delivery is of 25–35 mm when this limit is exceeded the ligaments rupture expecially the anterior one and then the rupture of the symphysis occurs According to the same author this phenomenon is more frequent in multiparas

The treatment is administered according to two policies (*a*) conservative (*b*) surgical

According to Cibils (2) absolute bed rest and tight pelvic binding seem to ensure complete recovery According to Trillat et al (3) and Charvet et al (1) the treatment has to be conservative by mobilization and hammock suspension dur period of three weeks when the space betwe two pubis bones according to X ray does not ceed 40 mm

In contrast in the cases in which the obstet pubic distraction is more than 40 mm the treat has to be surgical osteosynthesis of the pubis the aid of metallic cerclage

CONCLUSIONS

The syndrome of the ruptured symphysis pubis ing spontaneous delivery is very rare Tod



Fig 3

vere complications of delivery which were reported 30 years ago are no more seen In our case complete bed rest for 3 weeks and fixation with tight pelvic binding resulted in complete recovery

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ACTIVE PRE TFRM MANAGEMENT OF SEVERE OSTEOGENESIS IMPERFECTA

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stract Some of the advantages of using an intra mniotic injection of urea combined with prostaglandins mid trimester termination include an extremely high cess rate a mean time of approximately 10 hours and livery of a dead fetus The successful application of this thod for the active pre term management of patients in om severe fetal abnormality such as that reported here ggests this technique of inducing abortion and labour serves further consideration in those special circum nces where the obstetrician is anxious that the preg ncy should be interrupted despite the gestation length d where a live birth should not occur

recent years termination of pregnancy in the first d second trimester has been increasingly rformed on patients in whom suspected or proven al abnormality has been demonstrated as a result specific investigations including chromosome pat ns of amniotic fluid cells alphafetoprotein levels rasonography and rubella antibody titres though the range of abnormalities which may be ected in early pregnancy is likely to increase ne defects may not become apparent until late gnancy and then present the obstetrician with a ision as to whether to actively intervene or to ve the situation alone despite the emotional ess that the latter decision might engender

This report describes the active management of a ient in whom severe osteogenesis imperfecta was gnosed at 32 weeks

CASF REPORT

s D W aged 40 years booked for confinement at 10 ks gestation having had a normal delivery 10 years viously Amniocentesis was performed under asound control for alpha fetoprotein levels and chromosome constitution because of her age The alpha fetoprotein levels of the serum and liquor amnii were normal but poor growth of amniotic fluid cells prevented any conclusive report on the genetic status of the fetus

Serial ultrasound assessment of biparietal diameter *measurements indicated a satisfactory fetal growth rate* but the fetus was reported to be difficult to define The antenatal care remained uncomplicated until 3? weeks when polyhydramnios rapidly developed The biparietal diameter at this time was 8 45 cm and an apparent double echo was seen A straight X-ray of the abdomen showed that the only fetal parts visible were vague soft tissue outlines and parts of the vault of the skull The appearance was consistent with an extreme case of osteogenesis im perfecta

At 34 weeks one litre of amniotic fluid was aspirated because the patient became extremely uncomfortable Within 48 hours the situation had become exacerbated and difficulty with respiration was experienced The patient was aware both of the diagnosis and the prognosis of the condition and a decision was made to terminate the preg nancy in view of the predictable outcome and the degree *of polyhydramnios*

TECHNIQUE

Vaginal examination prior to the procedure revealed a long uneffaced cervix 3 cm dilated Amniocentesis was performed using a supra pubic drainage cannula (Bard International No SP1966) passed into the amniotic cavity under local anaesthesia with the bladder previously emp tied One litre of amniotic fluid was aspirated and then a solution containing 80 g urea (Ureaphil Abbot Laboratories) made up with 80 ml sterile Hartmann s solu tion was injected and followed by PGL_2 5 mg as described previously (2)

Uterine activity developed rapidly and the patient was sedated with intramuscular diamorphine 10 mg A grossly abnormal stillborn female infant weighing 2404 g was de livered 1 hour 46 minutes later

The external and radiological features of the fetus are shown in Figs 1 and 2 respectively The findings on post

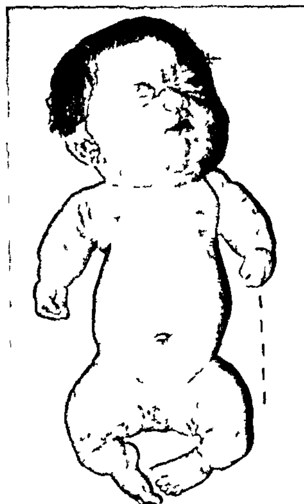


Fig 1 External appearance of fetus exhibiting severe steogenesis imperfecta

mortem examination included marked scalp oedema shortened limbs with very prominent skin creases bowing of the legs and a small thorax containing hypoplastic lungs The bony skeleton showed pronounced generalised osteoporosis with shortening and deformity of the long bones a softened cranial vault healed fractures and nor mal epiphyseal cartilages

Tubal ligation was performed on the third day and the patient made an uneventful recovery

DISCUSSION

Osteogenesis imperfecta is an inherited autosomal dominant disease with a high rate of spontaneous mutation presenting in varying grades of severity with defects in collagen containing tissues particularly involving skeletal bones (1 3) Less severely affected cases have thin bones which fracture after birth Deafness and blue sclera may be other manifestations More severely affected cases like one described here survive only a short time have multiple fractures and other abnormal fe... such as phocomelia Associated polyhydra... may be a feature (4)

A decision to induce labour before term in a tient with severe fetal abnormality can only be templated if the outcome of induction of labo be guaranteed The technique of using comb intra amniotic urea and PGE_2 as opposed to alternative methods e g extra amniotic p... glandins or more standard approaches such as niotomy and intravenous oxytocic stimul was selected because of the very high success ra... terminating mid trimester pregnancies found this method and because of the likelihood that severely affected fetus would not be born a...

Fig 2 X ray of the fetus showing osteogenesis and cient bone formation

alleviating additional distress Although live
uses have occurred following induction of mid
mester abortion using intra amniotic hypertonic
line and other agents none have been observed
th the standard dose of urea and variable amounts
PGE$_2$ which have been used to successfully
duce abortion without failures in over 130 cases
he dose of PGE$_2$ administered was empirically
lected as twice that currently being used for mid
mester termination because of the possible dilu
n effect of the excess liquor present The experi
ce obtained of using this method for induction of
bour in patients with other severe abnormalities
compatible with life including anencephaly sug
this may be the treatment of choice in such
uations

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ANNOUNCEMENTS

Symposium on Medical Genetics The Hungarian Society of Human Genetics will organize an International symposium with WHO support in Debrecen Hajduszoboszló Hungary 27–29 April 1976 Topics Cytogenetics population genetics prenatal diagnosis and genetic counselling *chromosomal mapping clinical genetics on the molecular* level hemoglobinopathies immunogenetics Further enquiries should be addressed to Human Genetic Laboratory H-4012 Debrecen P O Box 37 Hungary

XXIVth Annual Colloquium on Protides of the Biological Fluids is due to be held in Brugge 27 April – 1 May 1976 Topics Pregnancy associated proteins carcino fetal and carcino placental proteins detection and quantitation of proteins by molecular amplification Further information through Secretariate Simon Stevin Instituut Jerusalem straat 34 B 8000 Brugge Belgium

International Congress of Sexology Montreal 28–31 October 1976 Program Sex therapy sex education sexual dimorphism sex difference in erotism sexological aspect of contraception problems of ethics in sex therapy and sex investigation Co-sponsors Dept of Sexology of the University of Quebec in Montreal and Society for the Scıentıfic Study of Sex USA Further information Professor Robert Gemme Department of Sexology [versity of Quebec in Montreal C P 8888 Mont Quebec Canada H3C 3P8

C S Vott Center Colloquium in Andrology The C Mott Center for Human Growth and Development is h ing a colloquium on *Techniques of Human Andr* May 6–7 1976 at Wayne State University School of M cine Detroit Michigan Research papers on techn are accepted before February 1 1976 Invited pap *will deal with evaluation of testicular* biopsy ph biochemical and bacteriological tests of semen c chemistry of spermatozoa histochemistry of maa s organs ultrastructural localization of enzymes en' crine profiles and karyotyping of men clinical ex: tion of infertile men biochemical and immunol evaluation of prostate post coital tests freezing of se artificial insemination and behavioral therapy of s *sexual inadequacies Films* Sexual Therapy of S Inadequacies panel discussion (analysis of male m pause and erectile and ejaculatory disorders) Fo formation write to Dr E S E Hafez Departme Gynecology–Obstetrics 550 E Canfield Detroit 48201 (Tel 313/577 1011) Registrat on before Mar 1976 is for limited number

LETTER TO THE EDITOR

the article Study of glucose-6 phosphate and itrate dehydrogenases DNA RNA and total ogen in the rabbit placenta during its hyper ophic response to ovariectomy (Acta Obstet necol Scand *53* 209 1974) the authors state that increase in placental weight is apparently due hypertrophy rather than to hyperplasia as indi d by unchanged DNA The data however em to support an alternative explanation

review of the data shows that the DNA/g of ue (and presumably cell number) was similar in h control and experimental placentas as was the l nitrogen The DNA/total nitrogen ratio per placental weight is therefore unchanged ce there is no evidence of cellular hyper hy Furthermore since the placental weight was eased in the experimental group the total DNA l hence cell number) will be higher indicating cellular hyperplasia without hypertrophy ac nts for the increase in placental size

should be mentioned parenthetically that the n of the total number of fetuses or liveborn per r for each group is not included in the results e there is a negative correlation between litter ber and placental (and fetal) size it follows that any comparison of placental weight the mean number should be similar in the experimental control groups An evaluation of this point is possible However if the number of placentas is n as representing litter number then the mean ber of fetuses per litter in the experimental p would be 4 6 (37–8) vs 6 7 (47–7) in the rols a difference that could account for the r placentas in the former group It is fully zed that the above calculation is based on an assumption and hence may be in error but it serves to underscore the importance of taking litter size into consideration

That bilateral ovariectomy (probably prior to day 27) in pregnant rabbits leads to larger placentas (and fetuses) is now well established Our data show that the increase in placental size is limited to the fetal placenta and that cellular hyperplasia without a demonstrable change in cell size occurs We have further shown that this response is a function of the estrogen milieu (1–4)

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2 Abdul Karim Haviland M & Beydoun S N Placental hypertrophy in oestrogen deprived pregnant rabbits Oxford Medical School Gazette *24* 17 1972
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APPEAL

Information is required on a hypothesis concerning the sex of human zygotes For this purpose will anyone with data on the sex of any monoamniotic twin pairs please communicate with Doctor W James Galton Laboratory University College London W C 1 England

This appeal has been received from Doctor James who has an interesting theory concer the formation of the sex of the conceptus and needs material for his research in order to prove hypothesis

I S

Acta Obstet Gynecol Scand 55 87–93 1976

FIGO NEWS

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS (F I G O)

Secretariat Maternite 1211 Geneva 4 Switzerland

ABSTRACTS

...nutes of the 22nd annual meeting of the Executive ...rd of the International Federation of Gynecology and ...stetrics held on Sunday March 2nd 1975 in the ...nquet Hall of the West End Hotel Bombay India

...ttendance

24 Officers and Executive Board members 19 were sent or represented

...fficers (with special status) Dr B N Purandare ...ia) President Dr A Ingelman Sundberg (Sweden) ...e President Dr R Caldeyro-Barcia (Uruguay) Presi ...elect *represented by Dr C MacGregor (Mexico)* P Magnin (France) Treasurer represented by Dr de Watteville Dr H de Watteville (Switzerland) ...retary General Dr R Vokaer (Belgium) Deputy ...retary General Dr H A Kaminetzky (U S A) ...tor of the F I G O Journal—excused

...on rotating members Dr J Varangot (France) ...esented by Dr C Sureau Dr H Husslein (German ...eral Republic) Sir Stanley Clayton (Great Britain) Dr L Jhaveri (India) Dr S Sakamoto (Japan) Dr L ...telazo-Ayala (Mexico) represented by Dr C ...Gregor Dr K P Russell (USA) represented by H C Taylor Dr L S Persianinov (USSR) repre...ed by Dr T V Chervakova

...otating members Sir Lance Townsend (Australia) Dr ... Salvatore (Brazil)—excused Dr C Gomez Rogers ...le)—absent MUDr A Kotasek (Czechoslovakia) Dr H Mossadegh (Iran) Dr G J Kloosterman ...therlands)—excused Dr O Akinla (Nigeria) Dr S S ...iam (Singapore) Dr A Dominguez Gallegos ...nezuela)—absent

...ecial committees Dr C P Hodgkinson (USA) ...irman of the Committee on Annual Reports and ...nition of Terms in Human Reproduction—excused H Ulfelder (USA) Chairman of the Cancer ...mittee of F I G O—excused Dr R Contamin ...nce) Chairman of the Joint Committee for the Study Gynecological Problems in Childhood and Ad...ence represented by Dr L Rauramo (Finland) S Tomkinson (Great Britain) Chairman of the Joint ...y Group on the Training and Practice of Midwives Maternity Nurses—present Dr A Alvarez Bravo ...ico) Chairman of the Committee on Maternal ...tality Studies—excused Dr H C Taylor (USA) ...rman of the Committee on Medical Aspects of Human Reproduction—present Dr G Resauro (Italy) Chairman of the Committee on Perinatal Mortality—excused Dr P O Hubinont (Belgium) Chairman of the Committee on Qualifications—absent Dr F G Geldenhuys (South Africa) Chairman of the committee on the Reorganization and future Functions of F I G O—absent Dr O Kaser (Switzerland) Chairman of the Scientific Program Committee for the VIIIth World Congress—excused

Invited Dr P Muller (France) was invited to participate in the session when the item relating to gynecological problems in childhood and adolescence was discussed

2 *Agenda*

The provisional agenda was adopted after addition of item a[1]) Discussion of the draft amendments to the Bye Laws of F I G O concerning the Special Committees of the Federation and "F I G O s Relations with other international Organizations to point 4 of the agenda Secretariat of F I G O

3 *Minutes of the 21st annual meeting of the Executive Board*

The Minutes of the 21st session of the Executive Board held in London on July 6th 1974 were adopted with one minor change in wording related to Sir Lance Townsend s active participation in the work of the Perinatal Mortality Committee

4 *Secretariat of F I G O*

Report by the Secretary General Dr de Watteville (Switzerland) Secretary General of F I G O read his report on the activities of the Secretariat

In his report the *Secretary General* expressed appreciation to Dr Vokaer and his co-workers at the French speaking sub-secretariat of F I G O in Brussels for their most valuable cooperation thanks to which all relevant documents have been translated into French and dispatched to the 25 Societies wishing to receive F I G O s documents in this language For information Dr Vokaer s address is as follows Service de Gynécologie et d Obstétrique Hopital Universitaire Brugmann 4 place A van Gehuchten 1020 Brussels Belgium

The *Secretary General* furthermore added that the list of Heads of University Departments of Obstetrics and Gynecology and Directors of Research Institutes dealing with Human Reproduction is under re ision and will be

ready on time for the VIIIth World Congress in Mexico City October 1976 This document and the list of constituent Societies of F I G O with their addresses and the names of their Presidents and Secretaries are available at F I G O s Secretariat in Geneva

Links have been maintained with the World Health Organization as in the past and thanks were expressed to those colleagues who represented the International Federation at regional and Expert Committee meetings organized by W H O

Draft amendments to the Bye Laws of F I G O The draft amendments concerning the Special Committees of the Federation and the F I G O s Relations with other international Organizations were submitted by the *Secretary General* Both drafts were accepted without discussion and modification and will be submitted for ratification to the General Assembly in Mexico City

Committee on the Reorganization and future Functions of F I G O No report was received from Dr Geldenhuys (South Africa) Chairman of the Committee who was prevented from attending the meeting

The *Secretary General* read two letters received from Executive Board members and three from affiliated Societies in reply to Dr Geldenhuys report which had been dispatched to F I G O s constituency after the last Board meeting in July 1974

Further to a long discussion concerning the replacement of the Secretary General and after a formal vote it was decided that a small special Committee of Board members familiar with F I G O s activities and problems should after a thorough investigation set up a list of candidates for the post of Secretary General and prepare a detailed report on the problem of this succession to be handed over to the Nominating Committee as a guideline for its deliberations The following Board members were designated for this Committee Dr Ingelman Sundberg (Sweden) Vice President of F I G O as convenor Dr Geldenhuys (South Africa) Chairman of the Committee n the Reorganization and future Functions of F I G O Stanley Clayton (Great Britain) and the representative rance

5 *International Association for Maternal and Neonatal Health*

A report including a new draft for the Constitution of the International Association which will be formed by national sections as well as individual members was read by the *Secretary General*

The report was adopted and the possibilities for the Board members to help organizing the International Association were discussed The independence of the International Association vis à vis F I G O was stressed

The four members on the Scientific Council of the International Association to be designated by F I G O were nominated they are Dr Purandare (India) Dr Alvarez Bravo (Mexico) Dr Sakamoto (Japan) and Dr Sureau (France)

6 *Nominating Committee*

According to the Bye Laws the Nominating Committee for election at the next World Congress in Mexico City of the new Officers three rotating Board members and the Chairman and members of the Scientific Pr Committee for the IXth World Congress was appoi

Further to the following ex-officio members t Board members and three delegates of Socie represented on the Board were to be designated

Ex-officio members 1) Dr B N Purandare (I President of F I G O 2) Dr R Caldeyro-B (Uruguay) President-elect 3) Dr H de Watt (Switzerland) Secretary General

After a secret ballot the following *Board members* selected 4) Dr S Sakamoto (Japan) 5) Dr K P P (USA) 6) the representative of France

The following *Societies* were chosen for appo their delegate 7) Peru 8) Philippines 9) Poland.

The choice was made taking into consideration f representation on a Nominating Committee and g graphic distribution

7 *Finances of F I G O*

The report of the Treasurer Dr Magnin (France) presented by his proxy *Dr de Watteville* (Switzerland

As of December 31 1974 the financial situation sho credit balance of SF 237014 70 which means an incr of SF 74000 since December 31 1973 However increase is mainly due to the contribution of SF received from the Organizing Committee of the V World Congress in Moscow In 1974 F I G O spe 64298 05 for its activities (Secretariat and s Committees)

The budget for 1976 as suggested by the Treasurer amounting to SF 78000 was adopted without discus

In his report the Treasurer expressed his concern the devaluation of the US dollar since the contributions F I G O s constituency are paid in this currency and expenses mostly in Swiss francs Therefore he s ge that possibly the annual contribution should be in to US $1 50 per active member at the next Gen Assembly in order to face the continuous devaluation the dollar The *Secretary General* pointed out th devaluation of the Swiss franc is most likely to occ the near future After discussion it was decided a propose to the General Assembly an increase membership fee for the time being

The Treasurer s report shows that on the who contributions of the affiliated Societies are paid admissible time limits However there are Societies—grouping a small number of active m bers—which have not fulfilled their financial mitments towards F I G O for three or more despite repeated reminders sent out by the Secretar Geneva (three from Latin America two from Afr from Asia and one from Europe) According to a dec taken by the last General Assembly these Societies be formally excluded from F I G O s constituency now However the *Secretary General* s ggested those Societies which failed to pay their dues be December 31 1975 should not enjoy the extended to the members of affiliated Societies (re the participation in F I G O world congresses the registration fees right to present a voluntary comm participation of a delegation of the Society in the Gen Assembly) This suggestion was accepted

IIIth World Congress of Obstetrics and necology Mexico City October 17–23 1976

am ation of the Congress Dr MacGregor (Mexico) retary General of the Congress substituting for Dr stelazo-Ayala President of the Congress presented the gress report of the Organizing Committee while the t of the report was being distributed to the Board mbers present

The members of the Board expressed their deep preciation for the excellent work accomplished by Mexican colleagues and *Dr Husslein* (Australia) resentative of the German Federal Republic thanked m especially for the inclusion of German as an official ngress language during the main sessions The *retary General* expressed the satisfaction of the Board t Spanish English simultaneous translation will be ilable for all seminars and voluntary contributions

The registration fees as proposed by the Organizing mmittee were accepted they are up to April 15 1976 . $130 00 per active participant US $80 00 per ompanying member after April 15 1976 US $150 00 active participant US $100 00 per accompanying mber

t was furthermore specified that Congress participants belonging to an affiliated Society will pay an increased istration fee as follows up to April 15 1976 US 0 00 per Congress participant US $100 00 per ompanying member after April 15 1976 US $170 00 Congress participant US $1?0 00 per accompanying mber

The schedule for the meetings of the special committees October 14 & 15 1976 as prepared by the Secretary neral was discussed In spite of the inconvenience for committee members to reach Mexico City three days ore the opening of the Congress it was felt that there no better possibility The *Secretary General* was ed to inform the chairmen of the special committees as n as possible and request that they confer this rmation to their committee members

The *Secretary General* reported on his correspondence n the liaison officers of the International Society for the dy of Trophoblastic Disease and the International iety for the Study of Vulvar Disease Drs Goldstein di Paola and with Dr Ulfelder Chairman of the ncer Committee of F I G O relating to joint meetings h I S S T D and I S S V D will hold a meeting in xico City starting October 24 and therefore it would possible to hold a joint meeting with each of these ups on Saturday October 23 after the Closing emony of the F I G O World Congress Papers could ead on invitation by members of F I G O as well as bers of I S S T D and I S S V D and Congress icipants could attend the meetings by prolonging their in Mexico City of a few hours only

r MacGregor pointed out that it was already planned ave a correlated seminar on trophoblastic disease and this could possibly be transformed into a joint ting Another possibility would be to hold the tings on Wednesday afternoon as no other scientific vities are scheduled at that time While giving its ement on the principle of the joint meetings the Board it to the Secretary General of the Congress to make the necessary arrangements as he deems it best after having discussed the matter with Dr Goldstein for I S S T D and Dr di Paola for I S S V D as well as with Dr Ulfelder Chairman of the Cancer Committee of F I G O

The suggestion of the *Secretary General* to offer the Presidents of I S S T D and I S S V D an opportunity to deliver a speech during the last main session of the Congress on Saturday morning (October ?3) was not retained because the time schedule appeared already tight and the fear was expressed that this would create a precedent and that other small groups could expect the same privilege in future

Scientific Program of the Congress The scientific program as proposed by Dr Kaser (Switzerland) Chairman of the Committee was accepted with only two minor changes

It wa decided that all voluntary contributions should be screened by the national Society to which the author is affiliated March 31 1976 was accepted as deadline for handing over the abstracts of the papers announced to the local Organizing Committee

A special Seminar dealing with teaching of social obstetrics will probably be organized by the W H O Unit of Maternal and Child Health As the W H O budget for 1976 will only be voted in June 1975 no precise information is available at present The Board agreed upon the principle and entrusted the Organizing Committee with the task of making the necessary arrangements directly with Dr Petros Barvazian from W H O

Dr MacGregor expressed his willingness to seek financial means for making possible the participation in the Congress for a maximum of five speakers who have been invited by the Scientific Program Committee and who have no funds for making the trip to Mexico

9 *Journal of F I G O*

Dr Kaminetzky (USA) Chief Editor of the International Journal of Gynaecology and Obstetrics was unable to attend the Board meeting but his report had been circulated among the Board members prior to the meetings The agreement between F I G O and the new publisher Almqvist & Wiksell (Stockholm) was approved

Unfortunately *Dr Ingelman Sundberg* (Stockholm) could not obtain the publisher's agreement for bulk subscriptions at a lower subscription rate

The *Secretary General* pointed out that in its present form the Journal is not of any great use for F I G O as no income coming from the Journal can be expected in the near future and as the Journal contains very little material relating to F I G O s activities It is not likely that the number of paying subscribers will soon exceed 1 500 the more so as the Journal is rather duplicating already existing national journals instead of developing features of its own and promoting the idea of international exchange of information

The *Secretary General* expressed his deep regrets that the abstracts of the last Executive Board meetings have not been published in the Journal

Dr Kaminetzky s suggestions of having special issues of the Journal on a precise subject prepared by a guest-editor invited for this task was well received by the Board These

special issues should contain contributions written on invitation by experts in a given field and representing various geographic areas

Dr Taylor put forward the idea that the Journal could mainly be devoted to a particular aspect of our specialty which is not dealt with by other journals As an example Dr Taylor quoted social aspects in teaching and practice of Obstetrics and Gynecology

The Board members felt that it was mandatory to appoint an editor at the place where the Journal is published in order to facilitate continuous and close contacts between the publisher and the Editorial Board Therefore *the Executive Board elected unanimously Dr Ingelman Sundberg Associate Editor of the Journal*

Taking up an idea put forward by the Norwegian Society of Obstetrics and Gynecology the *Secretary General* was asked to prepare newsletters on F I G O s activities such as abstracts of Board meetings special committees activities etc which should be circulated among the affiliated Societies with the request that they inform their members and possibly publish part of the newsletters in their own journals The wish was expressed that this material of information should also be sent directly by the Secretariat to important journals as it is already done at present (French Mexican Argentine Indian journals)

10 *Cancer Committee of F I G O*

Dr Ulfelder (USA) Chairman of the Committee was prevented from attending the meeting and had sent a report containing the following important points

Volume 16 of the Annual Reports will be published and distributed prior to the VIIIth World Congress in October 1976

Results of treatment for cases of cancer of the cervix rpus vagina and *ovary* treated through 1968 will be rporated in this volume

e Cancer Committee has reviewed the staging thod for cancer of the ovary and has approved on some changes which will be put before the General Assembly 1976 for ratification

Minor changes in the staging instructions for cancer of the cervix have been elaborated by the Committee and will be dispatched to all collaborators in the Annual Reports They will also be presented to the General Assembly in Mexico City

The former project of staging for cancer of the vulva has been reviewed by the Cancer Committee and no changes were recommended Therefore the General Assembly in Mexico City will be asked to ratify it and results of treatment for cancer of the vulva will be included in Volume 17 of the Annual Reports

The Cancer Committee of F I G O has maintained contacts with the International Society for the Study of Vulvar Disease and the International Society for the Study of Trophoblastic Disease

The Committee has also maintained links with the Commission on clinical oncology of the International Union Against Cancer (U I C C) the American Joint Commission on Staging and End Results reporting the Committee on Oncology of the A C O G and with other bodies concerned with gynecological cancer

It is hoped that a joint meeting of representatives of these working committees may take place around the time of the VIIIth World Congress in order to arrive at a concensus towards a solution of the minor differences in staging procedures which now exist

The members of the Cancer Committee are Dr L A Arrighi (Argentine) Dr J Bonte (Belgium) Dr K Hashimoto (Japan) Dr H Husslein (Austria) Dr P Kolstad (Norway)—Vice-Chairman Editorial Committee of the Annual Reports Dr H L Kottmeier (Sweden)—Chairman Editorial Committee of the Annual Reports Dr K A McGarrity (Australia)—Vice-Chairman Cancer Committee Dr J H Maus (Canada) Dr I D Netchajeva (USSR) Mr R B Rickford (Great Britain) Dr H Ulfelder (USA)—Chairman Cancer Committee Dr J P Wolff (France)

11 *Committee on Qualifications*

Dr Hubinont (Belgium) Chairman of the Committee was prevented from attending the meeting and unfortunately had not sent a report

However the Executive Board discussed at length the organization of a Seminar devoted to Post-Graduate Training in Obstetrics and Gynecology to be held on the occasion of the VIIIth World Congress in Mexico City

Dr Ratnam (Singapore) accepted to be the President of the Seminar and to organize it in cooperation with the local Organizing Committee and more especially with MacGregor Secretary General of the Congress

The Executive Board agreed upon the following preliminary schedule for this Seminar

The Seminar will take place on Sunday October 17 1976 one session to be held before the Opening Ceremony and the second one afterwards

The Societies affiliated with F I G O will be invited to send delegates to the Seminar

The Seminar will be limited to the discussion of post graduate training and the main themes will be

1) the training of the specialist should comprise Gynecology as well as Obstetrics

2) specific requirements for the training of such specialist should be established and the qualification of the specialist be recognized by a diploma

3) the participants in the meeting should express their opinion on the minimal and the optimal duration of training for obtaining this diploma

4) a point of view should be expressed on the mode of training taking into consideration the time allotted to practical and/or theoretical training

5) how should the level of knowledge and the ability of the trainee in the practice of Gynecology and Obstetrics be controlled? Examinations? Evaluation of the trainee's performances (work) by his monitors?

6) the value of refresher-courses for the specialists after they have obtained their diplomas

It is hoped that the participants in the meeting will agree on recommendations concerning the various points mentioned above These recommendations would be submitted to the General Assembly after having been accepted by this gathering The resolution of F I G O would be addressed to all those concerned with training specialists in Obstetrics and Gynecology such as the

ithonties medical associations university authonties

In order to avoid fruitless discussions rapporteurs will designated for various regions of the world These pporteurs will prepare a report on the conditions for ialification in Obstetrics and Gynecology prevalent in eir part of the world These reports will be read during morning s session of the Seminar and will be followed a general discussion on each item mentioned above d to the drafting of a recommendation to the General sembly

It appeared that the cooperation of several members on Committee on Qualifications was rather poor and refore Dr Hubinont has been approached with the quest to co-opt new active members with the agreement the President of F I G O Dr Purandare

Dr *Ratnam* was nominated Vice-Chairman of the mmittee on Qualifications

Committee on Annual Reports and Definition Terms in Human Reproduction

Hodgkinson (USA) Chairman of the Committee was ortunately prevented from attending the meeting but l sent a report on the activities of the Committee he is ning

r Hodgkinson had planned to publish a small booklet distribution to the constituent Societies of F I G O oducing the medical terms relating to perinatal and ernal mortality which have been approved in Moscow 973 and which will probably be included in the XIth sion of the International Classification of Dis s prepared by the World Health Organization ortunately the cost of such a publication was pro- tive and for the moment the idea had to be given up ne of the main future tasks of the Committee will be preparation of a list of definitions in order to collect orm data concerning perinatal morbidity and mortality ch would be published as annual reports following the rm of the Annual Reports on the Results of Treatment arcinoma of the Uterus Vagina and Ovary edited by Kottmeier (Stockholm) The first step will be to are a list of definitions and criteria to be used by the tutions which would be willing to submit their reports e Committee

order to work out uniform definitions contacts been established with the American College of tetricians and Gynecologists the Royal College of tetricians and Gynaecologists and the French Society Obstetrics and Gynecology which have already ared similar lists

Joint Study Group on the Training and tice of Mid es and Maternity Nurses

Tomkinson (Great Britain) Chairman of the Com e presented a report on the activities of the Joint ly Group

1973 and 1974 four Working Parties have taken in San Jose for the countries of Costa Rica temala El Salvador Nicaragua Honduras and ama in Yaounde for the countries of Cameroon Central African Republic Gabon Republic of 30 Zaire and Malagasey Republic in Nairobi for the countries of Kenya Ethiopia Uganda Tanzania Zambia Botswana Lesotho Swaziland and Mauritius and finally in Bridgetown for the countries of Barbados Belize Dominica Grenada Guyana Haiti Jamaica Trinidad and Tobago Senior midwives obstetri cians pediatricians experts and consultants in Family Planning—Nutrition participated in these Working Parties W H O and I P P F were also represented The conditions for obstetrical care and means of promoting it were discussed at the Working Parties and a Field Director was appointed for each region The Field Director will make follow-up visits to all countries concerned to see how and if the recommendations made at the Working Parties are being implemented

A similar meeting was held in Bogota Colombia in January 1975 at which all South American countries were represented by an obstetrician and two or more midwives The group of 50 people discussed during 10 days better organization of obstetrical care In those countries where there is rivalry between midwives and obstetricians it was possible to dissipate anxieties and the Working Party ended in an atmosphere of great friendliness and mutual desire to identify and recognize the traditional birth attendant so as to provide her with some training in hygiene family health and nutritional problems

Working Parties are planned for South Asia East Asia India Oceania and North Africa

A meeting of International Confederation of Midwives and F I G O Joint Study Group representatives will take place in London in July 1975 to complete arrangements for publication of the revised edition of "Maternity Care in the World

The Joint Study Group continues to receive financial assistance from the United States Agency for Inter national Development

The Joint Study Group continues to cooperate with and receives assistance from the UN International Children s Emergency Fund the World Health Organization the International Planned Parenthood Federation and the International Pediatric Association

The members of the Joint Study Group are Dr J S Tomkinson (Great Britain)—Chairman Joint Study Group Miss M Bayes (Great Britain)—Secretary Joint Study Group Dr A Alvarez-Bravo (Mexico) Dr A Cardenas (Colombia) Dr B Faris (New Zealand) Dr V Hingorani (India) Dr G J Kloosterman (Netherlands) Dr E Leinzinger (Austria) Dr R Willson (USA)

14 *Committee on Maternal Mortality Studies*

Dr Alvarez Bravo (Mexico) Chairman of the Committee was unfortunately unable to attend the meeting but had requested *Dr MacGregor* to kindly present his report on the activities of the Committee which contains the following important points

The Committee is working on the edition and publication of a Pamphlet on Maternal Mortality Studies in English French German Spanish and Italian including 1) definitions classifications and rates on maternal mortality 2) setting up and functioning of Maternal Mortality Committees 3) reporting on maternal deaths form for that purpose and instructions how to compile the report

At present the pamphlet is being translated from English into the other languages The final and definite manuscript should be ready by the end of this year The Committee and its central office in Mexico are doing any effort to have this pamphlet ready for distribution and sale for the 1976 World Congress

In the meantime the Committee is taking care of any request for information on Maternal Mortality Studies and is sending adequate material printed in mimeograph *(duplicator) in English and Spanish*

The Committee has assisted the setting up of Maternal Mortality Studies Committees in Colombia and Costa Rica

The World Survey on Maternal Mortality Studies is going on with success Fortunately the prestige of the F I G O Committee has increased and now the Committee is receiving spontaneous communications on the statistical data of diverse committees

15 *Committee on Perinatal Mortality*

The *Secretary General* announced thatDr Tesauro (Italy) Chairman of the Committee has recently undergone a *surgical treatment and though being convalescent he* could not attend the meeting

Dr de Watteville recalled that the present objective of the Perinatal Mortality Committee is the collection of data for the preparation of annual reports on perinatal mortality This publication would include uniform statistics on perinatal mortality received from big obstetrical departments as well as national statistics if available This problem was discussed and it was felt that the Committee should request the cooperation of the World Health Organization and the Committee on Annual Reports and Definition of Terms in Human Reproduction (see page 10 of this document) which could greatly help *the Perinatal Mortality Committee in the realization of this* ject

The Board decided to appoint a Vice Chairman of the ttee with responsibilities *Dr Kloosterman* therlands) accepted this post

16 *Committee on Medical Aspects of Human Reproduction*

Dr Taylor (USA) Chairman of the Committee commented on his report which had previously been sent to the members present

The principal work of the Committee during the last year has continued to be the completion of the teacher s Manual on Reproductive Physiology Elementary Demography and Family Planning

The final manuscript consists of fifteen chapters or lectures with a total length of about 600 manuscript pages *accompanied by 450 illustrations The present plan is to* have two so-called editions The first or teacher s edition will have a loose leaf format and its illustrations will be duplicated by a set of lantern slides Of this edition there will be 1 500 copies published one half with slides The other edition perhaps properly called the student s edition will be firmly bound still in three volumes but without lantern slides Of the student s edition there may be 5 000 copies printed and of course at a much lower cost

A grant has been obtained to provide free of teacher s edition with slides to Departments of Obs and Gynecology in developing countries that signif interest and intent to use the Manual The stu edition however will be for sale by the Massach Institute of Technology Press at the low estimated $6 00 or $6 50 for each of the three volumes of the

In his report *Dr Taylor* furthermore propose teaching seminars be organized in various parts *world with selected members of the Committee pre* each The idea seems especially promising now sin seminars would include a consideration of the Manu the presentation of sets to departmental representat

Dr Purandare (India) was appointed Vice-Chairn the Committee

17 *Joint Committee for the Study of Gynecological Problems in Childhood and Adolescence*

Dr Rauramo (Finland) substituting for Dr Con (France) Chairman of the Committee presented a on the activities of the Joint Committee

The Committee is presently organizing an In tional Symposium devoted to the Study of Gynecol Problems in Childhood and Adolescence to be h Lausanne (Switzerland) from March 25–27 1976 main themes of the Symposium are puberty of th *contraception and pregnancy in the adolescent* surgical treatment of genital malformation There wi be a program of free communications

In his comments *Dr Rauramo* explained that contacts should be established with the World H Organization As an example a report from the W consultation on Pregnancy and Abortion in Adolesce in the process of being finalized A close cooperation W H O would be very useful to the Joint Committ the Study of Gynecological Problems in Childhoo Adolescence and it would be easier to arrange a m of the Committee as a workshop together with W Should the results of the workshop be interesting en *it might also be possible to* publish a W H O book the workshop because the questions of gynec problems in childhood and adolescence are of i international interest

Furthermore the Joint Committee is trying to e closer contacts with pediatricians

The Board appointed *Dr Rauramo* new Chair the Joint Committee in replacement of Dr Con nominated Honorary Chairman

The new Chairman was *entrusted* with co members for his Committee which should be cons of gynecologists and pediatricians since pediatrici starting a new Association both in USA and Eur *the study of adolescence in general*

Finally the name of Dr Dewhurst (Great Britai suggested as the Vice Chairman of the Committee

18 *Varia*

The International Federation received *invitations* t a representative to the following meetings

(*a*) XVIIth International Congress of M Lausanne (Switzerland) June 21–28 1975—co *by the International Confederation of* Midwi

omlinson (Great Britain) Chairman of the Joint Study roup on the Training and Practice of Midwives and Maternity Nurses agreed to be F I G O s representative n this occasion

(b) World Conference of the International Women s ear Mexico City (Mexico) June 19–June ? 1975—rganized by the United Nations in New York *Dr acGregor* (Mexico) accepted to represent F I G O at is Conference

(c) International Conference for the Ninth Revision f the International Classification of Disease Geneva (Switzerland) September 30–October 6 1975—convened by the World Health Organization *Dr Ingelman Sundberg* (Sweden) agreed to participate in these meetings as F I G O s representative

19 *Next executive Board meeting*

The next Board meeting of F I G O will take place in Mexico City on Saturday October 16th 1976 the day prior to the Opening Ceremony of the VIIIth World Congress of Obstetrics and Gynecology

INFORMATION RECEIVED BY F I G O ON THE FOLLOWING CONGRESSES

fth European Congress of Perinatal Medicine Uppsala eden June 9–12 1976 Themes Socio-economic pects of perinatal medicine breech delivery diabetes d pregnancy continuous monitoring of mother fetus d newborn infant For information contact the Secretariat of the Congress P O Box 1 S 750 14 Uppsala 14 weden

th National Scientific Congress of The Israel Society Obstetrics and Gynecology Tel Aviv Israel June 22– 1976 Themes Infections in Obstetrics and Gynecoy surgical trends in gynecology medical and surgical mplications in pregnancy Free communications Symposium on gynecological oncology For further information contact Professor R Toaff c/o Organizing Committee of the Congress P O Box 16?71 Tel Aviv Israel

Fifth International Congress of Endocrinology Hamburg German Federal Republic July 18–24 1976 The Scientific Program includes plenary sessions symposia sessions and short communications In addition there will be workshops and special sessions For information contact The Congress Organizer Congress Reiseburo Hamburg Fifth International Congress of Endocrinology D-?000 Hamburg 36 Marseiller Strasse . German Federal Republic

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INCREASING CAESAREAN SECTION RATE

H E Johnell H Östberg and T Wåhlstrand

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tract At the University Hospital in Uppsala 719 sarean Sections (C S) were performed 1966–1970 total number of deliveries was 16 708 The C S rate eased from 7 0% to 7 8% This trend was mainly due an increasing frequency of C S performed for halopelvic disproportion fetal distress bad obstetrical ory and failed induction of labour with intravenous tocin drip No maternal deaths occurred The natal mortality was 5 0% In infants with a birth ght of 1 500 g or less the perinatal mortality was 57% in infants with a birth weight of more than 2 500 g and stational age of 37 weeks or more it was 0 9% In 07 tive C S on healthy mothers at term no perinatal ths were noted

ring the late 1960 s a remarkable increase of the rate was observed in many Departments of tetrics and Gynaecology in Sweden (3 5) The of the present investigation was to study varia s in the indications for C S in connection with a fold increase in the C S rate at a Swedish versity Hospital and to study the influence of increase on maternal and fetal mortality and bidity

MATERIAL

719 C S performed at the University Hospital in sala during 1966–1970 were studied (Table I) This ital is a Regional Hospital The present series might egarded as representative for a Swedish Central nty Hospital with the exception that 20 C S were ormed on Rh immunized mothers referred to the ital from other districts

METHODS

records of the patients delivered by C S were re ined with reference to maternal age obstetrical ry indications for C S operative technique opera and post-operative complications anaesthetic iods Apgar score recorded one minute after birth birth weight gestational age perinatal mortality and neonatal morbidity Only the main indication was re corded in each case even if other indications were stated in the record An X ray pelvimetry was made in all cases delivered by C S for cephalopelvic disproportion The capacity of the pelvic outlet was judged from the sum of the interspinous diameter the intertuberous diameter and the sagittal outlet diameter (1 2) Patients with a true conjugate of the pelvic inlet of less than 9 5 cm or a sum of the outlet diameters of less than 29 5 cm were considered to have a contracted pelvis Patients with a true conjugate of the pelvic inlet of 9 5–11 0 cm or a sum of the outlet diameters of 29 5–31 5 cm were classified as borderline cases (4) Previous operations on the uterus i e classical C S myomectomy or Strassman s operation were classified as uterine scar Indications such as multipara without living child long standing infertility multiple spontaneous abortions and previous complicated deliveries were called bad obstetrical history Abnor mal fetal presentations were sub-divided into three groups 1) breech presentation in elderly primipara 2) transverse lie and 3) other malpresentations Breech pre sentation was always combined with other indications such as elderly primipara uterine inertia cephalopelvic disproportion diabetes or fetal distress These cases were recorded as the indication combined with breech presenta tion Lower segment incisions transverse or longitudinal as well as classical incisions were used Hysterectomy was performed only for special indications In some cases sterilization was carried out by division of the Fallopian tubes

All patients were anaesthetized by a trained anaesthetist 0 5 mg of atropine was used as pre medication The basic method of anaesthesia was induc tion with nitrous oxide–oxygen and pentothal sodium An endotracheal intubation was performed with suc cinylcholine relaxation which was the method of muscle relaxation until the delivery of the fetus and the placenta The patient was ventilated with nitrous oxide–oxygen 1 1 until the delivery The anaesthesia was then con tinued with artificial ventilation with nitrous oxide–ox ygen 3 1 with curare relaxation and the analgesia was completed by pethidine or in a few cases halothane methoxyfluorane or diethyl–ether In 15 cases the pentothal sodium was replaced by propanidid and in 17 cases diethyl–ether was added during the induction In

Table I Incidence of Caesarean Sections (C S) and perinatal mortality for infants delivered by C S at the University Hospital in Uppsala 1966–1970

Year	Deliveries (*n*)	C S (*n*)	C S (%)	Perinatal mortality (%)
1966	3 409	68	2 0	11 8
1967	3 450	104	3 0	2 9
1968	3 509	122	3 5	7 3
1969	3 217	181	5 6	2 7
1970	3 173	244	7 8	4 4
1966–1970	16 708	719	4 3	5 0

one case of eclampsia nitrous oxide and halothane were used for the anaesthesia as barbiturates and pethidine in high doses were used in the treatment of the patient prior to the C S

Body temperature of more than 37 0°C in the morning or of more than 37 5 C in the afternoon after the third post operative day in cases treated with antibiotics was recorded as puerperal fever if no specific explanation was found in the record

The perinatal mortality was defined as the sum of the number of stillborn infants with a gestational age of more than 28 weeks and the number of infants who died within 7 days of birth

All infants were immediately taken care of by a paediatrician who estimated the Apgar score one minute after birth Infants with an Apgar score of 7–10 were considered vigorous those with 4–6 slightly depressed and those with 1–3 severely depressed

The infants were classified according to Yerushalmy (9) The 5 groups recommended by him are defined in Table V

All infants delivered by C S were observed in the Department of Paediatrics at least 24 hours after the delivery The causes of perinatal deaths were confirmed by post mortem examinations in all cases In infants with neonatal morbidity the diagnosis was made by a paediatrician Minor congenital malformations and slight neonatal hyperbilirubinaemia were not taken into consideration

In order to estimate the risk for the infant at C S special attention was paid to a group of elective C S performed on healthy mothers at term

RESULTS

The C S rate increased about 4 times during the period under investigation (Table I) while the number of deliveries was fairly constant Altogether 683 women were operated on 649 once 32 twice and 2 three times No maternal deaths occurred after C S or after vaginal deliveries during this period

The distribution into different age groups was fairly constant during the period of investigation The maternal age at C S was on an avera years 55% of the women operated o primigravidae A slight increase in the freq primigravidae was seen during the last 2 yea number of women with three or more previ liveries decreased from about 9% in 1966 to 1970 The relative frequency of patients wi ous abortions C S or operative vaginal de was fairly constant As a comparison to the given it can be mentioned that the mean m age at delivery was 26 3 years in 7190 deliv the Department during 1967–1969 (7) Wi Uppsala Hospital Region 42 4% of the wome primigravidae out of 96753 deliveries 1964–1968 (8)

Cephalopelvic disproportion was the mo mon indication (Table II) This indication in about 4 times in frequency Forty patients contracted pelvis 229 had a border line pelv 11 had a normal pelvis according to the defi The frequency of all three types of pelv higher at the end of the period than at t among patients delivered by C S for cephal disproportion Fetal distress and bad ob history were in 1970 about 10 times more fr than in 1966 as indications for C S Psychia cations were noted only the last two year immunization and transverse lie were mo mon during the last year Many indicatio placenta praevia abruptio placentae d other malpresentations and prolapsed u cord showed no upward trend toward the en period

Additional indications were stated in ab fifth of the cases without any significant va during the period

It was noted that attempts to induce labo an intravenous oxytocin drip were given w increasing frequency and C S performed i Thus emergency C S were performed in ca fetal distress occurring in connection with o drips once in 1966 and 12 times in 1970 increasing number of cases (5 11 12 8 respectively) C S was made when an oxyto and in some cases artificial rupture o membranes failed to induce labour The were recorded under the indication for th tion of labour

Lower segment transverse incisions we 685 times and lower segment longitudinal 2 Classical incisions were made 7 times fo

ble II *Indications for Caesarean Sections at the University Hospital in Uppsala 1966–1970*

	1966	1967	1968	1969	1970	1966–1970
phalopelvic disproportion	??	38	57	79	84	280
al distress	5	11	14	3?	47	109
l obstetrical history	?	2	5	17	19	45
centa praevia	4	14	1?	3	6	39
ruptio placentae	3	8	10	6	1?	39
betes mellitus	9	6	5	8	9	37
immunization	4	4	6	3	1?	29
ther malpresentations	7	5	2	5	7	?6
laemia	1	3	2	5	6	17
nsverse lie	2		1	4	8	15
primigravida	3	1		6	4	14
lapsed umbilical cord	1		4	4	?	11
rine inertia	1	1	1	2	5	10
rine scar			1	3	3	7
chiatric indication				1	5	6
tmaturity				1	3	4
id cervix	1	1			1	3
ital malformation					3	3
vious vaginal plastic surgery		1			?	3
ch presentation in erly primigravida		2				?
inent uterine rupture	1			1		?
s		1	1			2
rt disease		1	1			
tructed birth canal		1				1
ellaneous	2	4		1	6	13

cations such as transverse lie placenta praevia cervical cancer Hysterectomy was performed nes once for atonic bleeding once for placenta reta and once for bilateral bleeding from the ine arteries Injuries to the urinary bladder oc red 6 times and an intestinal injury once iough 103 patients were operated on previously i C S a dehiscence of an old uterine scar was i only once Bleeding exceeding 600 ml was d in 164 cases In 32 of these cases bleeding irred prior to the C S Sterilization was com d with C S 10 times

one case a serious complication of anaesthesia irred After the injection of 250 mg pentothal ium and 75 mg succinylcholine bronchospasm noted together with an acute laryngeal oedema spasm of the vocal cords which was not re d by additional succinylcholine Treatment i 100 mg hydrocortisone and 0 3 mg adrenaline given with prompt effect The patient was deli d under local anaesthesia of the abdominal wall nitrous oxide–oxygen inhalation The infant vigorous with an Apgar score of 8

i uncomplicated post-operative course was in 581 (81%) of the mothers Puerperal fever noted 45 times (6 3%) endometritis 25 times (3 5%) and urinary infections 13 times (1 8%) Wound complications occurred 42 times (5 8%) Venous thrombosis was seen once No pulmonary embolism occurred (Table III)

The number of infants was 726 twins occurred 7 times The infants were vigorous at birth in 86% slightly depressed in 6% and severely depressed in 8% (Table IV) Infants with a low one minute Ap gar score had a considerably higher neonatal mor tality than other infants All enonatal deaths oc curred in cases anaesthetized with the basic method of anaesthesia In cases with variations of the basic method i e adding diethyl ether during the induc

Table III *Maternal complications after delivery by Caesarean Section at the University Hospital in Uppsala 1966–1970*

Puerperal fever	45
Wound complications	4?
Endometritis	?5
Urinary infections	13
Bronchopneumonia	4
Paralytic ileus	3
Pneumothorax	?
Eclampsia after delivery	1
Venous thrombosis	1
Miscellaneous	5

Table IV *Neonatal deaths in relation to Apgar score one minute after birth by Caesarean Section at the University Hospital in Uppsala 1966–1970*

Apgar score	Infants (n)	Neonatal deaths n	%
7–10	6?0	9	1 5
4– 6	42	6	14
1– 3	56	13	23

tion of anaesthesia or replacing pentothal sodium by propanidid the frequency of low Apgar scores did not differ from the total series

The number of stillborn infants was 8 (Table V) In 5 of these cases the infant was thought to be alive immediately before the C S In 3 cases the fetus was known to be dead but the C S was performed for another important indication The total perinatal mortality was 5 0% It was higher in the first year than during the rest of the period The perinatal mortality was highest in Group I and lowest in Group V If the infants were sub divided only according to birth weight the perinatal mortality was 24% in Groups I–III and 2 1% in Groups IV–V

The perinatal mortality in all deliveries at the Department during the same period was 1 9% (0 7% for infants with a birth weight of more than 2 500 g and 27% for infants with a birth weight of 2 500 g or less)

The most common cause of neonatal death after ...very by C S was idiopathic respiratory distress syndrome (IRDS) (Table VI) In 5 of the 13 deaths in IRDS erythroblastosis was also present No infants in Group V died from IRDS Congenital malformations were equally distributed over ... Groups Cerebral haemorrhage was only se... Group V In the case of placental infection ... membranes ruptured 7 days before the C S

Neonatal morbidity was diagnosed in ... (16 5%) of the live born infants

The number of elective C S perform... healthy mothers at term was 207 (29%) The n... elective C S increased more than the total ... rate Twins occurred once Two infants had a b... weight of less than 2 500 g Most of the ?08 inf... were vigorous at birth but 6 were slightly a... severely depressed Neonatal morbidity was se... 11 infants (5%) but all survived the neonatal per... IRDS was diagnosed in 2 infants aspiration ... infants hypoglycaemia in 2 infants and pulm... atelectasis in 1 infant One of the twins had ... ficulties in maintaining a normal body tempera... Congenital hydrocephalus in one infant ... diagnosed prior to the C S by X ray

DISCUSSION

The incidence of C S for different indicatio... present investigation is compared with th... previous study (6) in Table VII It is evident ... number of C S performed for placenta ... toxaemia transverse lie old primigravida... nent uterine rupture and heart disease were ... unchanged The frequency of these indicati... also stable during the period of the present ... gation This was also true for the ind... abruptio placentae diabetes mellitus and ... *malpresentations but these indications we...* common in the present investigation than

Table V *Stillborn infants and neonatal deaths in connection with Caesarean Sections at the U... Hospital in Uppsala 1966–1970*

The infants were classified according to Yerushalmy (9)

Infant group	Birth weight (g)	Gestational age (weeks)	Infants (n)	Stillborn (n)	Neonatal deaths (n)	Perinatal mortality (%)
I	1 500 or less	All ages	7	1	3	57
II	1 501–2 500	Less than 37	68	2	13	2?
III	1 501–2 500	37 or more	20	2	2	?0
IV	2 501 or more	Less than 37	72	1	7	11
V	2 501 or more	37 or more	559	2	3	0 9
I–III	2 500 or less	All ages	95	5	18	?4
IV–V	? 501 or more	All ages	631	3	10	? 1
I–V	All weights	All ages	726	8	28	5 0

-vious one As regards uterine scar breech pre ntation in elderly primigravida and obstructed th canal a decrease was seen

The entity bad obstetrical history as defined in present investigation may be widened to include l primigravida breech presentation in elderly migravida and uterine scar In that case an in ase from 31 2 per 10000 deliveries during the)0 s (6) to 40 7 in the present investigation was n In fact the incidence of such cases was lower ring the first 3 years of the present investigation d higher during the last 2 years

The indications that were most responsible for increased C S rate were cephalopelvic dispro- tion fetal distress and bad obstetrical tory An increase was also noted in the number patients who had been exposed to attempts to uce labour prior to the C S Three causes may be ponsible for these changes Firstly increased ntion to the possibility of cephalopelvic dispro tion and to the previous history during the enatal period secondly more active obstetrics h increased attention to deviations from the mal progress of labour and signs of fetal distress thirdly a tendency to give up an attempt to ice labour when there was no response to one or intravenous oxytocin drips and in some cases ficial rupture of the membranes The situation be summarized as an attempt to reduce the ards of delivery The perinatal mortality in den is low The death of an infant during deliv is regarded as a disaster Thus C S are formed with increasing frequency in order to id complications in labour

e VI *Causes of neonatal deaths after arean Section at the University Hospital in sala 1966–1970*

nfants were classified according to Yerushalmy (9) lefinition of the infant groups see Table V

	Infant groups					
	I	II	III	IV	V	I–V
athic respiratory ess syndrome	1	6	1	5		13
iroblastosis alis		5		1		6
ormation		1	1	1	1	4
oral haemorrhage					2	2
turity	2					2
ntal tion		1				1

Table VII *The incidence of Caesarean Section for some indications per 10000 deliveries in the County of Kopparberg 1951–1960 (6) and at the University Hospital in Uppsala 1966–1970 (present investigation)*

	County of Kopparberg 1951–1960	Present investigation
Cephalopelvic disproportion	5? 6	167 6
Fetal distress	3 6	65 2
Bad obstetrical history	5 3	?6 9
Placenta praevia	21 8	?3 3
Abruptio placentae	5 0	23 3
Diabetes mellitus	10 3	22 1
Other malpresentations	4 4	15 6
Toxaemia	11 7	10 [illegible]
Transverse lie	8 1	9 0
Old primigravida	11 7	8 4
Prolapsed umbilical cord	0 5	6 6
Uterine inertia	3 8	6 0
Uterine scar	8 9	4 2
Psychiatric indication		3 6
Breech presentation in elderly primigravida	5 3	1 2
Imminent uterine rupture	1 7	1 2
Heart disease	0 5	1 2
Obstructed birth canal	3 ?	0 6

The perinatal mortality at C S was lower in the present investigation than during the 1950 s in the County of Kopparberg (6) In the latter study the results at the Central County Hospital (Group A) were better than in the whole County and more comparable to those of the present investigation In A in the first series all mothers with Rh immunization were excluded If the same procedure were made in the present investigation the perinatal mortality would be 3 6% (1 7% for infants with a birth weight of more than 2500 g and 19% for in fants with a birth weight of 2500 g or less) Thus the perinatal mortality was obviously lower in the present investigation This may to some extent be due to wider indications for C S but also to im proved prenatal care of the mothers and neonatal care of the infants

The group of elective C S performed on healthy mothers at term may mirror the risk for the infant at delivery by C S No perinatal mortality was noted and the neonatal morbidity was lower than in the total series However neonatal morbidity was observed in 5% of these infants The most serious complications was IRDS in 2 cases The risk for an infant may be lower at a normal vaginal delivery than at a C S But who can guarantee to a pregnant

woman that her delivery will be a perfectly normal one?

Was the increasing C S rate justified? It is very difficult to give an answer on the basis of the present study The intention with almost every C S was to secure not only a living but also a healthy infant Furuhjelm (5) studied C S in cases of fetal distress *She followed up the babies through child* health centres Such a follow up might be the best way to solve this problem which was outside the aim of the present study

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DISTRIBUTION OF BLOOD FLOW IN MYOMATOUS UTERI AS MEASURED BY LOCALLY INJECTED 133XENON

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stract Regional blood flow in the myometrium and omata has been measured during laparotomy in 11 pa its using locally injected 133Xenon Blood flow was culated from the wash-out curves using both initial pe technique and compartment analysis Assuming ial partition coefficients in myometrium and myomata following values in ml min 100 g are seen ial slope technique—myometrium 15 6±2 79 my ata 5 1±0 95 compartment analysis—myometrium 01±3 21 myomata 5 5±1 16 The blood flow was al /s lower in myomata than in myometrium of the same rus The main reason for the reduction of blood flow unit weight of uterus in patients with myomata previ ly reported thus seems to be low blood flow in the omata A slight reduction of blood flow in the sur nding myometrium however also seems probable

ı previous study (7) using the isotope clearance hod it was shown that blood flow per unit ght of myomatous uterus is reduced in compari with non myomatous uterus Similar conclu ts can be drawn from a study by Klingenberg This is believed to be the result of an impaired od flow within the myomata Clinical experience in agreement with this idea Degenerative nges in uterine myomata are frequent and are ught to reflect insufficient blood supply How r morphological data indicate great variations in ularity in myomata (3 4 8 13)

urthermore the blood vessels of the surrounding metrium are affected by the myomata This t was described by Sampson (14) and in a more nt study by Farrer Brown et al (2) By com sing veins myomata may impair drainage of the ounding myometrium and endometrium This t may lead to pathological uterine bleeding It also lead to a reduction in blood flow in normal metrium surrounding myomata Thus the observations cited above (7 10) may depend on a generalized slowing of blood flow in the myomatous uterus as a whole blood flow in myomata and the surrounding myometrium being of about the same magnitude They may also be the result of a very low blood flow in myomata and only a slight or no reduction in the perfusion of the surrounding myometrium Previous studies do not give any in formation on blood flow within myomata as com pared with normal myometrium in the same uterus The present work was intended to compare within the same uterus and at the same occasion blood flow in myomata and in the intervening myo metrium

METHODS AND MATERIAL

The isotope clearance method utilising 133Xenon was used The theoretical details have been described in pre vious papers (5 6 1?) The injection technique has been that described by Jansson (9) All measurements were made during laparotomy with the uterus exposed 0 1–0 15 ml of a solution of 133Xenon dissolved in 0 9% NaCl solution was injected via the uterine serosa In a few cases a smaller volume was used—identical volumes injected into both myomata and myometrium In myomata the injection depth varied with the size of the tumor but in all cases the isotope was deposited well inside the capsule of the myoma The injections into normal myometrium were made at a depth of 0 5 to 0 7 cm from the serosa The needle was as a rule held obliquely to the surface to ensure a needle track of at least 0 7 to 1 cm The injection needle had an outer diameter of 0 4 mm No aspiration was made prior to isotope injection Injection time was 20 sec and the needle was left in situ for another 20 sec in order to minimize the risk of leakage through the needle track Recording was carried out as described for intraarterial injections (5) In all cases at least two recordings were carried out Since remaining isotope from previous in jections might interfere with following recordings old

isotope depots were shielded with lead so that they were not seen by the detector.

Two types of curve analysis were performed. The initial slope method for curve analysis was applied on all curves using the initial portion of the curve but disregarding any steep fall of the curve immediately after removal of the isotope syringe and needle from the visual field of the detector. Compartment analysis was performed when the elimination curve was of the multi exponential type. In order to calculate total blood flow of the labelled region the compartments were weighed together by taking the percentage of activity at the end of the injection as judged by extrapolating curve components to time +20 sec. This percentage is a measure of the relative size of compartments within the labelled tissue volume. Regional uterine blood flow (RUBF) then has been calculated according to eq. 1

$$\mathrm{RUBF}=\frac{A_1F_1+A_2F_2}{100} \qquad (1)$$

where A_1 and A_2 stand for percent radioactivity at time +20 sec in compartments 1 and 2. F_1 and F_2 are blood flows in compartments 1 and 2. The validity of this type of curve analysis has been discussed in a previous paper (6). In all calculations of blood flows the partition coefficient of skeletal muscle 0.7 (1) was used.

The patients were undergoing radical or conservative surgery because of myomata. Anaesthesia was of the routine type excluding halothane. A semi open non rebreathing system was used to prevent rebreathing of isotope. Blood pressure was within normal limits during the operation. The cases are presented together with results in Table I.

Statistical analysis was carried out using a pairing design test (16).

RESULTS

In 11 patients a total of 25 measurements we[re] carried out. From normal myometrium only [?] out of 11 curves were of the mono-exponential ty[pe]. The rest were multiexponential curves.

In 14 recordings from myomata 12 were of the monoexponential type and only 2 multiexpo[-] nential. Curve analysis according to the in[itial] slope method (Table I) gave as a rule lower val[ues] than the compartment analysis (Table II). In [the] statistical analysis of values according to i[nitial] slope a statistically significant difference was se[en] between normal myometrium and myo[mata] ($p<0.001$). If curves are analyzed according to t[he] compartment method even greater differe[nces] result. Myomata always had lesser perfu[sion] than normal myometrium. Mean b[lood] flow ± standard error of the mean in myomata [was] 5.1 ± 0.95 ml min^{-1} 100 g^{-1} and in myometr[ium] 15.6 ± 2.29 ml min^{-1} 100 g^{-1} when calcula[tions] are made from the initial slope of the curve. [If] compartment analysis is carried out the values a[re] for myomata 5.5 ± 1.16 and for myometr[ium] 20.0 ± 3.21 ml min^{-1} 100 g. No correlation [be-] tween myoma size and blood flow was se[en]. Neither was there any correlation between b[lood] flow in myomata and normal myometrium in [the] same uterus. Two myomata had a multi-expone[ntial] wash out curve. One of them was in fact

Table I. *Blood flow (ml min^{-1} 100 g^{-1}) in myometrium and myomata according to initial slope*

Pat	Age	Phase of cycle	RUBF myometrium	Type of curve	Size of myoma	RUBF myoma	Type of curve	Remarks
F E	46	Prolif	16.7	Multiexp	3 cm	11.0	Monoexp	
G A	43	–	34.7	Multiexp	5 cm	0.5	Monoexp	
A E	31	Prolif / secr	20.2	Multiexp	? cm	5.1	Monoexp	Small volume of isotope
					3 cm	1.0	Monoexp	
L S	40	Secr	14.3	Multiexp	10 cm	4.3	Monoexp	Small volume of isotope
P O	42	–	15.6	Multiexp	? cm	8.9	Monoexp	
					5 cm	8.5	Monoexp	
W B	51	–	6.9	Monoexp	1 cm	1.8	Monoexp	Small volume of isotope
					5 cm	3.8	Monoexp	
S I	?8	Prolif	10.8	Multiexp	8 cm	4.4	Multiexp	Adenomyoma
J I	46	–	9.7	Multiexp	5 cm	0.6	Monoexp	Pelvic varic[es]
J R	48	Secr	6.2	Monoexp	6 cm	5.6	Monoexp	
L A-G	44	Secr	21.1	Multiexp	10 cm	11.8	Multiexp	
I B	49	*Prolif*	15.6	*Multiexp*	*4 cm*	4.4	Monoexp	
Mean			15.6			5.1		
S E M			?.29			0.?5		

able II *Blood flow (ml min⁻¹ 100 g⁻¹) according to compartment analysis in cases with multi tponential curves*

at	Measured region	Quick component	Slow component	~ quick component	RUBF
E	Myometrium	53 9	7 6	45 7	28 8
A	Myometrium	44 1	17 3	81 8	39 2
E	Myometrium	53 9	14 9	39.3	30 2
S	Myometrium	24.3	9 ?	48 9	16 6
O	Myometrium	25 6	10 2	49 8	17 7
I	Myometrium	19 4	8 5	17 2	10 4
I	Adenomyoma	19 4	0 8	29 0	5 4
I	Myometrium	?8 5	7 7	27 1	13 3
A-G	Myometrium	44 1	13 1	65.5	33 4
A-G	Myoma 10 cm	30 3	7 1	41 5	16 7
B	Myometrium	22 1	8 8	64 6	17 4

enomyoma. Both belonged to the largest tumors the series Several myomata showed slight de nerative changes according to the pathologist s port but no case of necrotic myoma was in ided

DISCUSSION

is clearly shown that myomata in this study have significantly lower blood flow than normal ometrium in the same uterus This seems to be in reement with clinical observations and rphological data The main reason for the low rine blood flow in myomatous uteri in the studies Klingenberg (10) and Forssman (7) thus seems to low blood flow within the myomata From the sent study the effect of myomata on the perfu n of surrounding myometrium cannot be luated The recorded blood flow values for ometrium are low compared to those of Jansson For a reliable comparison however it would be essary to have groups that were comparable h respect to age parity hormonal status and hnique of isotope injection Such factors do not rfere with the conclusions of the present study e each patient is her own control as we compare fusion of myometrium and myomata

lood flow in myomata seems to be homogene in most cases In only two out of 14 measure nts was the wash-out curve of the multi onential type Furthermore one of these tumors not a simple myoma but an adenomyoma wever the fact that myomata can show a multi onential elimination curve indicates that there may exist well and less well perfused compartments within the same tumor When the well perfused portion is of very small weight as compared with the less well perfused the graphical separation of curve components becomes difficult The same applies when perfusion rates are of similar magnitude Thus it may be that different components are not discovered by the present type of curve analysis It must also be stressed that the only thing really measured is the elimination of isotope from the labelled part of the tissue If a small non representative volume of tissue is labelled false conclusions may be drawn from the resulting wash-out curve when results are extrapolated to the whole organ or tissue The present study very distinctly points out one potential risk in the use of the isotope clearance method for the study of uterine blood flow This is the risk of injecting isotope into a myoma not representative for the bulk of uterine tissue When injections are made under the control of the eye and the palpating hand during laparotomy this risk is small When injections are made via the uterine cavity (5 12 15) or via the vaginal fornices (11) this danger is increased By taking special care in cases with myomata and by making repeated injections with different positions of the injection needle this risk would seem to be diminished

The partition coefficient has been taken to be 0 7 which holds true for most non fatty tissues If major variations occur between myomata and myometrium the conclusions concerning differences in blood flow may not hold true This factor clearly needs to be controlled

The present study also gives some information on

the problem of the anatomical counterparts of the components of the elimination curve after local and intra arterial injections of isotope In most cases in this study myometrium had two clearly separated components Most myomata had one component that was not identical with either of the other two This would theoretically result in a three component curve after intra arterial injections of isotope A few three-component curves were seen after intra arterial injections in myomatous uteri In these cases however the first component was of a magnitude never seen in the present study The obvious conclusion is that the two components usually calculated are the weighed means of families of similar perfusion rates This does not invalidate the calculations of RUBF based on the compartment analysis but the calculations of relative weights of tissue corresponding to the different blood flows becomes unimportant

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A PROSPECTIVE STUDY OF DRUGS AND PREGNANCY

II *Anti emetic drugs*

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stract In a prospective study of anti-emetic drug use ring 6 376 pregnancies the previously demonstrated gative correlation between the use of such drugs and scarriage was confirmed It is probably completely due less frequent and possibly less severe morning sickness mplaints in pregnancies ending with a miscarriage A ght positive correlation is found between the use of ti emetics and infant malformation A detailed analysis owed that this was mainly due to a high incidence of ug use (mainly promethazine) among women giving th to infants with congenital dislocation of the hip The obable indirect relationship is discussed

the first paper in the present series (5) factors ociated with the use of psychopharmaca during gnancy were discussed based on a prospective dy of drug use in pregnant women in Malmo ried out during 1963–65 The present paper re ts a similar study of anti-emetic drugs (mainly ihistamines) based on the same material The sible hazards of antihistamine drugs have been ch discussed They are used mainly during early gnancy when morning sickness is common and anogenesis takes place and they have been used a vast number of pregnant women Soon after thalidomide tragedy suspicions were raised inst some drugs with anti emetic properties ably meclozine (9) The general opinion now is t no teratogenic effects can be demonstrated but ecent study on diphenhydramine by Saxen (7) reopened the question

MATERIAL AND METHODS

detailed description of the material and methods used reader is referred to the first paper of this series (5)

RESULTS

Spontaneous and induced abortion

Fig 1 compares the use of anti-emetic drugs during the different pregnancy months in four groups of women women who will have a miscarriage (417) women who will have an induced abortion (158) women who will give birth to a dead infant (133) and women who will give birth to a live infant (5620) The curve for women who will later mis carry obviously lies below the others especially during months III–IV Women who will later have an induced abortion do not differ from women who will have a live infant In order to evaluate the statistical significance of these differences the use of anti-emetic drugs during the third month was compared between women who will have a living normal infant—591 used anti-emetics out of 4 954 women (11 9%)—and women who will later have a miscarriage—22 used anti-emetics out of 423 (5 2%) A χ^2 test gives $\chi^2=17\,5$ at 1 d f $P<0\,001$

Antiemetics are nearly exclusively used because of morning sickness Such complaints were re ported in 212 of 423 women who will abort (50%) and in 3 645 of the 4 954 women who will have a living normal child (74%) The reduced frequency of morning sickness in women who will later mis carry may be part of an explanation to the low intake of anti emetics A comparison of the groups using the frequencies of 22/212 (10 4%) and 591/3 645 (16 2%) instead gives $\chi^2=5\,3$ at 1 d f $0\,05>P>0\,02$

Further details of the association between vari ous factors and the presence of morning sickness

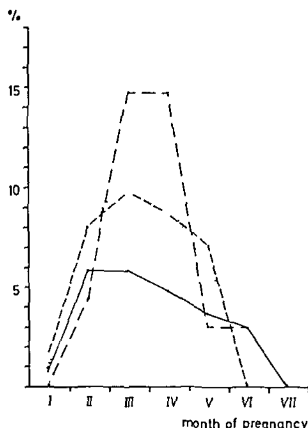


Fig 1 Percentage of women using anti-emetic drugs during different months of pregnancy according to pregnancy outcome ——=miscarriage – =induced abortion =live infant =dead infant

the use of anti-emetics are given in Table I The mean age of women who do not report morning sickness is significantly higher than that of women with morning sickness (t=3 1 P<0 001) but there is no significant difference between those who have morning sickness but do not use anti-emetics and those who use such drugs (t=1 1 N S)

The percentage of wanted pregnancies is significantly lower among women not having morning sickness than among women who report this complaint (χ^2=54 6 P<0 001) There is however f difference from this point of view between d users and non users (χ^2=2 3 N S) but the tre toward a higher incidence of wanted pregnancies *the former group This would fit with a correla* between desire for pregnancy and mornin ness A similar trend is of course also seen in the percentage of women married at LMP—increa from the group reporting no vomiting to a m imum in the group using anti emetic drugs (χ^2 at 2 d f P<0 001)

In order to study whether these factors exp the difference in the frequency of morning sick between women who miscarry and women who have a child these two groups were split accor to civil status (married at LMP or not) and desire pregnancy Table II gives the results The dif ence in the frequency of morning sickness betw the two groups of women is consistent in all gr but the effect of desire for pregnancy within c status is apparent and the effect of civil s *within the groups of wanted or unwanted p* nancies is also seen but is perhaps less clear

Apparently pregnancies which end in miscar are less prone to morning sickness than p nancies which result in the birth of a ch Perhaps also those women in the former gro do report morning sickness have less severe c plaints than such women in the latter group T could explain the remaining under representa anti emetics in the group of potential miscarr Another possible explanation is that civil s and/or desire for pregnancy influence the tim first contact with a gynecologist This prob analysed in Table III for women who will b live normal child It can be seen from th T that both factors act together—an increased f quency of early visits (during the first trimest

Table I *Some characteristics associated with morning sickness and use of anti emetics*

	No morning sickness	Morning sickness but no anti emetics	Anti-emetics
No of women	1 797	3 705	894
Mean age of women with S E M	6 85±0 17	26 14±0 08	26 38±0 17
% wanted pregnancies	76 1	83 6	85 7
% married at L M P	58 8	62 6	68 8

able II *Morning sickness civil status and desire for pregnancy All women who gave birth to a live ormal infant or who had a miscarriage*

	% of women reporting morning sickness			
	Married at L M P		Not married at L M P	
	Wanted pregnancy	Not wanted pregnancy	Wanted pregnancy	Not wanted pregnancy
iscarriage	56 1	45 8	5 9	36 8
ving normal child	75 1	69 6	7_ 8	70 9

en in the most positive group—married at MP with a wanted pregnancy This group will refore have a slightly increased chance of having ti-emetics prescribed and this could be one cause the higher intake of anti-emetics in pregnancies hich continue to term than in pregnancies ending miscarriage

ant death and malformations

Fig 1 there is an indication that women who will e birth to a dead infant used more anti-emetics pecially during the third and fourth month of gnancy than women who will have a live infant ? shows a similar tendency for women who will ve infants with major malformations while the up with infants with minor malformations agrees atively well with the normal group Fig 3 com es the best group—normal live infants—with tal group of perinatal pathology including h infants with major malformations and infants ch die before the age of one The difference is in noticeable

able IV shows use of anti-emetics during the t trimester in different categories Again a sur of anti emetic usage can be found in the group of major malformations but it does not reach statis tical significance (χ^2=1 9 at 1 d f) At least part of this explanation can be that morning sickness is more common among women who will have a mal formed infant (178/200=89%) than among women who will have a normal infant (3 680/5 002=73 6%) This difference is statistically significant (χ^2=23 9 at 1 d f P<0 001) The percentage of women who have morning sickness but do not use anti-emetic drugs is thus also increased in the major malforma tions group (72% compared with 60% in the control group χ^2=81 2 at 1 d f P<0 001)

Another approach was made in comparing the use of anti-emetics and the birth of malformed or dead infants 194 infants with major malformations and 194 matched controls were compared (for an account of the method of matching see (5)) and 93 infants who died before one year of age (53 were stillborn) were compared with 93 matched con trols The results are shown in Table V Among the mothers of dead infants the use of anti-emetics was in this sample even lower than among the controls but the tendency to increased anti-emetic use among women who had malformed infants re mained and even reaches statistical significance

le III *Time of first contact with a gynecologist civil status and desire for pregnancy among women gave birth to a normal live infant*

statu	Desire pregnancy	No of women with first visit to a gynecologist During 1st trimester	After 1st trimester
ied at L M P	Wanted	806 (8 5%)	2 0?0
	Not wanted	49 (?0 7%)	188
narried at L M P	Wanted	?6? (?1 0%)	986
	Not wanted	94 (0 %)	37

6 9 at 3 d f P<0 001

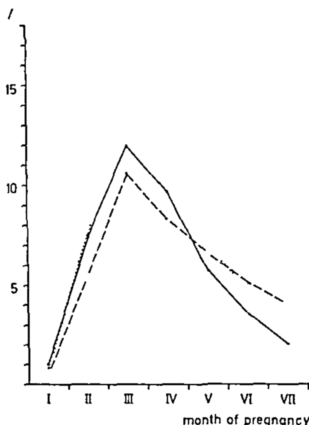


Fig 2 Percentage of women using anti-emetic drugs during different months of gestation Comparison between normal infants (——) infants with minor (------) and infants with major ( ) malformations

= 0 1 at 1 d f 0 025 >P>0 01) Morning sickness was more common in the malformation group (178 of 194) than among the controls (144 of 194)

The controls for the malformed infants selected in this way show a lower than expected incidence of drug usage when compared with the total group of women giving birth to normal live infants The reason for this is not clear—a similar phenomenon was seen in the analysis of psychopharmaca usage and was discussed briefly then(5)

Table V also shows the use of anti-emetics among women who bore infants with certain types of malformations The actual numbers are small but there is one group which shows a markedly high usage of anti-emetic drugs namely women whose infants have congenital dislocation of the hip (CDH)—there are 37 such women and 13 of these used anti-emetic drugs (11 of them promethazine) during the first trimester instead of the 4 expected Only 2 of 35 women who had infants with congenital heart disease had used anti-emetics

Fig 4 shows the incidence of women with morning sickness women with morning but not using promethazine and women promethazine comparing three groups when infants had CDH when they had other malformations and when they had no malformations at all The high incidence of promethazine users in the first group is evident—the incidence somewhat higher in the group of other malformations compared with controls but this small difference becomes still more reduced when the number of drug users is referred to the number of with morning sickness 11% in the malformation group and 8 3% in the control group (16 of 12 of 144 resp) This small difference is no more than random variation It cannot be concluded however that the slightly raised incidence of 11% in the malformation group might random variation *below* a truly significant At P=0 05 a doubling of the true malforma

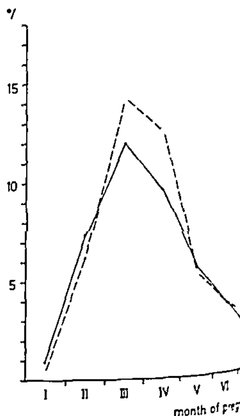


Fig 3 Percentage of women using anti-emetics during different months of pregnancy Long normal (——) compared with the group of pregnancy i e stillbirths and infants with major malformations (– –)

ble IV *Use of anti emetic drugs during the first trimester by women who had a normal infant or an ant with different kinds of malformations*

ant gory	Total number	Number using anti emetics	Numbers using drugs containing: Pro-methazine	Prochlor perazine	Diphen hydramine	Meclozine
	5 753	778	617	91	46	19
mal	5 00_ (87 0%)	679 (87 0%)	538	81	39	18
or malform	551 (8 6%)	65 (8 4%)	5?	8	4	1
gnif major lf	105 (1 7%)	?3 (3 0%)	16	?	3	0
ss major malforma	95 (1 5%)	11 (1 4%)	11	0	0	0

nce can still be hidden However we conclude except for the congenital dislocations of the no correlation between drug use and malfor on probably exists

nancy length and birth weight

difference is demonstrable in the duration of mancy (Table VI) or birth weight at term (Table) between pregnancies ending with the birth of a nal infant with and without anti-emetic drug use ng the first trimester

DISCUSSION

Women who are destined to have miscarriage—but not those that will have an induced abortion—use anti-emetic drugs less extensively than women who are going to give birth to a live infant This is partly due to the fact that women who will miscarry experience morning sickness less frequently than women who will have an infant as was also pointed out by Yerushalmy & Milkovich (10) When a correction was made for the different frequency of

e V *Number of women using anti emetics in general and prometha ine in particular during the first ster Infants with major malformations and matched controls infants without malformation but dead n one year with matched controls*

cted numbers calculated from the incidence of anti-emetic users in the total group of women giving birth to normal ts (679/5 00) or from all controls

l group	Total number	Number using anti-emetics	Expected no from total group	Number using promethazine
r malform	194	3	6 3	7
rols for major malform	194	16	6 3	12
but not malformed	93	10	1_ 6	7
ols for dead but not malformed	93	15	1 6	10
and/or major malf	87	4?	38 9	34
ontrols	87	31	38 9	
fc nalfo mat on types			*Expected no from all controls*	
s malform	11	3	1 _	-
lip and/or palate	10	0	1 1	0
heart malform ± other malf	35		3 8	2
spadias	15	3	1 6	3
dyspla ia of hip	37	13	4 0	11
ple malf	10	0	1 1	0
Down	10	2	1 1	1

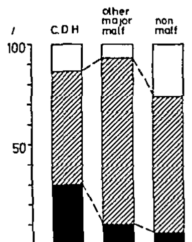


Fig 4 Percentage of women using anti-emetics (black columns) with morning sickness but not using anti emetics (hatched columns) and without morning sickness (empty columns) Women whose infants had congenital dysplasia of the hip (CDH) compared with women whose infants had other major malformations and with women who had normal infants

morning sickness a slight and just statistically significant difference was still left It could be claimed that this difference is also an artefact and due to differences in social factors or perhaps to differences not only in the incidence of morning sickness but also in the severity of the complaint when present

The discussion has helped to clarify an apparent protective effect of the drugs That such an effect would really exist is perhaps unlikely Similar considerations should be applied when an apparent harmful effect of a drug exists This can be exemplified by the correlation between the use of anti emetic drugs and the birth of infants with major malformations Previously Villumsen (1970) also found a higher consumption of anti-emetic women who go on to have a malformed in pared with women who have a norm whereas the opposite was found by Forfar (6)

One explanation could be that mornin occurs more often in pregnancies endin birth of a malformed infant than in norm nancies Doring & Hossfeld (4) claimed th en with hyperemesis gravidarum run an i risk of having a malformed infant In the study it was shown that there is an increase in drug users but also in women havin sickness but not using drugs when the major malformations is compared with the group of normal infants

A more detailed analysis shows that an drugs—mainly promethazine—were mainly one group of women namely those whc infant with congenital dislocation of the hip The cause of this abnormality is probably c one important factor being the endocrine s ing the pregnancy (1) It may be that gene are also implicated However it is hard t stand how a drug administered durin trimester could cause this abnormality likely explanation would be that the endoc turbance causing the CDH al o somehow in more severe vomiting and therefore in the likelihood of drug usage The incidence of sickness is not increased in the CDH gro compared with the group of other major m tions (32 instead of 33 expected) but the cc could be more severe

According to textbooks in ob tetri vomiting is more prevalent in conditions w

Table VI *Duration of pregnancy when anti emetic drugs were and were not used durin the first Normal infants according to sexes*

	Total number	Less than 38 weeks	38–42 weeks	More than 4 weeks	χ^2 (d f)
Boys					
With drug	340	29	302	9	9 N S
Without drug	049	15	1 806	91	
Girls					
With drug	339	?	307	10	0 ? N S
Without drug	2 035	139	1 83	67	

χ^2 between drug groups within sexes 3 1 at 4 d f N S
N S =non significant

ble VII *Birth weight among normal infants when the woman had or had not used anti emetic drugs ing the first trimester*

	Total number	Birth weight kg						χ^2(5 d f)
		<2 5	2 5–3	3–3 5	3 5–4	4–4 5	>4 5	
s								
– h drug	340	7	40	106	114	64	9	8 1 N S
hout dru	2 049	82	209	674	728	297	59	
s								
h drug	339	9	48	127	114	35	6	7 4 N S
hout drug	2 038	95	330	801	617	156	39	

etween dru groups within sexes = 15 5 at 10 d f N S
=non significant

adotropin (HCG) level such as hydatidiform le and twins HCG levels are often low in women n the time preceding a miscarriage (3) which ld fit with the observation that vomiting is in uent during pregnancies ending with a mis iage CDH is six times more frequent in girls n in boys (1) A significant correlation has been nd between sex of the conceptus and the blood adotropin level of the mother (3) with a higher l when the fetus is female Such an indirect hanism is one possible explanation of the find of increased promethazine use in women who later have an infant with CDH

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THE INTRAVENOUS INFUSION OF PROSTAGLANDIN $F_2\alpha$ IN THE MANAGEMENT OF INTRAUTERINE DEATH OF THE FETUS

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tract Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) was given in enously in the treatment of 16 cases of intrauterine th Delivery was achieved without complications or effects in 15 out of the 16 patients A posterior cervical in one patient treated with cervical dilata and $PGF_2\alpha$ infusion

.ases of intrauterine death safe methods are re red for the induction of labour For medical and chological reasons delivery is desirable as soon he diagnosis is made

n this study it is shown that prostaglandin $F_2\alpha$ $F_2\alpha$) can be used for the induction of labour in es of fetal death in the third trimester of preg y

PATIENTS AND METHODS

'een patients were carrying a dead fetus after 196 or e days of pregnancy The estimated mean duration ntrauterine death was 5 9 days with a range from 1 to days

most cases amniotomy was done primarily $PGF_2\alpha$ administered as a solution in normal saline by a ard pump infusion through a cannula in a forearm $PGF_2\alpha$ was given at an initial rate of 40 mcg/minute creased by hourly increments until a maximum dos 80 mcg/minute

RESULTS

en out of the 16 patients were delivered success The average induction-delivery interval was 7 s and 36 minutes (Table I) Complications oc d in none of the cases Except for a local ion in the infused vein side effects such as ea vomiting diarrhoea or pyrexia were not rded There was one case of failed induction re the start of infusion vaginal examination re d an elongated firm cervix Lovset s cervical instrument was used for mechanical dilatation of the canal $PGF_2\alpha$ infusion produced strong contrac tions After 10 hours vaginal examination revealed an unchanged cervix and the infusion was stopped Amniotomy was performed the following day and Hartel s dilatators were used together with $PGF_2\alpha$ for 40 hours Pelvic examinations then revealed a completely effaced cervix with a 2 cm rigid external cervical os A short time after a fetus was found emerging from the vagina Inspection revealed an intact cervical os and a transverse posterior cervical laceration The placenta was delivered through the laceration A repair was carried out vaginally the patient was given antibiotics and no postoperative complications occurred

DISCUSSION

There is good evidence for the value of the prostaglandins as agents for induction of labour in cases of intrauterine death The infusion of prostaglandin E_2 (PGE_2) has been reported by Karim (4) and by Filshie (2) In these series the mean infusion-delivery intervals were 12 or 8 hours re spectively but side effects such as nausea vomiting and diarrhoea were common

A simultaneous intravenous infusion of PGE_2 and oxytocin seems also to be effective and the incidence of gastro intestinal side effects is reduced (5) Another valuable alternative in the treatment of intrauterine death is the extra amniotic administra tion of the prostaglandins $F_2\alpha$ or E_2 (1)

The present study suggests that the intravenous infusion of $PGF_2\alpha$ for the induction of labour in cases of intrauterine death is a valuable method In 15 out of 16 cases the induction was successful the mean infusion-delivery interval was 7 hours and 36

Table I *Prostaglandin $F_2\alpha$ intravenous infusion in 15 successful cases with intrauterine death of the fetus*

	Mean±S D	Range
Maturity (days)	238±28 20	196–303
Prostaglandin $F_2\alpha$ total dose (mg)	20 3±11 80	2 7–44 4
Infusion delivery interval (hours minutes)	7 36±4 09	1 15–15 45

minutes and gastro intestinal side effects were avoided

In one case of unsuccessful induction a posterior cervical rupture occurred in association with the infusion of PGF_2 Similar accidents are reported following intra amniotic administration of $PGF_2\alpha$ for mid trimester abortion (3 6 7) In our case the infusion had lasted for 50 hours and should have been abandoned earlier

ACKNOWLEDGEMENT

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A NEW TECHNIQUE FOR THE LOCALIZATION OF THE CERVIX AT ^{113m}IN PLACENTAL SCINTIGRAPHY

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ract Sixty women in the third trimester of pregnancy examined with ᵐIn placental scintigraphy because eeding In 4 of the cases the scintigraphic procedure initiated by application of a Meyers ring containing n round cervix In the other cases the fundus and symphysis pubis were marked by means of a small active source Complete placenta praevia was cor y detected in 8 cases and marginal placenta in 4 cases scintigraphic localization of the placenta was correct in e women where the ring was used whereas when the nal marker was used seven errors occurred The ors therefore recommend this new technique in order ilitate the evaluation of the scintigrams

alization of placenta in cases of antepartum norrhage can be accomplished with different edures e g plain film radiography thermo- hy amniography and scanning with isotopes trasound Among these isotope and ultrasound ning are the safest and most reliable Drukker (1) d a correct diagnosis in 26 of 28 patients by nal counting after the intravenous administra of radio iodinated serum albumin Use of a nacamera shortens the procedure thus mini ng the risk of caval syndrome Recently 113ᵐIn ı (^{113m}In) has been introduced as an excellent ning agent for placenta localization and experi with this method has been reported by several ors (? 3 4 5) This study presents the results ᵐIn placenta scintigraphies including a new od of cervical marking carried out during a ır period (1972–73) in our departments

MATERIAL AND METHODS

women in the third trimester of pregnancy were ned with ^{113m}In placenta scintigraphy The women all suspected cases of placenta praevia because of bleeding In ?4 of the cases the scintigraphic procedure was initiated by application of Meyers ring containing 100 μCi ^{3m}In round the cervix in order to mark precisely this important anatomical region (Fig 1) Before placing the intravaginal marker 50 μCi ^{3m}In was placed in each of the two holes in the solid plastic ring In no case has the application and removal of the ring caused bleeding or other complications In 36 cases the fundus and the symphysis pubis were marked by means of a small radioac tive source

^{11} ᵐIn was eluated from a ^{3}Sn generator with dilute HCl (0 1 N) The raw eluate was used and 1 mCi of ᵐIn was administered intravenously Scintigraphy was carried out 10–15 minutes after injection The women were examined by means of a Pho/Gamma HP gammacamera Anterior and both lateral views were collected on Polaroid films A total of about 50 000 counts was obtained for each view using a high energy (410 KeV) diverging collimator and with a discriminator set to accept photons around 393 KeV ᵐIn has a physical half life of 1 7 hour and emits a single

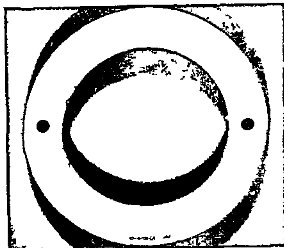


Fig 1 Meyer s ring In each of the two holes 50 μCi ᵐIn is applied and the holes are closed with a strip

Table I *Results of* ¹¹³ *In placenta scintigraphy in 60 patients*

	Technique for marking			
No of patients	*Pubic* symphysis	*Meyers* ring	Scintigraphy	Final diagnosis
8	4	4	Complete placenta praevia	Complete placenta praevia caesarean
1	1		Marginal placenta	Complete placenta praevia caesarean
4	2	2	Marginal placenta	Marginal placenta caesarean section
1	1		No placenta praevia	Marginal placenta caesarean section
1	1		Complete placenta praevia	Normal attachment of placenta vaginal d
4	4		Marginal placenta	Normal attachment of placenta vaginal
41	23	18	No placenta praevia	Normal attachment of placenta vaginal d
60	36	24		

gamma ray of 393 keV When injected intravenously ^{113m}In is associated with transferrin and this complex circulates throughout the blood including the placenta with very little transfer across the placenta to the fetus The biological half life of ^{113m}In in the blood has been found to be 6 7 hour (2) The absorbed dose received from 1 mCi ^{113m}In to the total maternal body has been calculated to 17 mrad to maternal blood 146 mrad and fetal blood 8 mrad (2)

RESULTS

Table I shows the results of ^{113m}In placental scintigraphy compared with diagnosis in 60 women The final diagnoses were obtained by vaginal delivery or by Caesarean section Complete praevia was correctly detected in 8 cases (Fig marginal placenta in 4 cases One complete praevia was interpreted as marginal placenta ar marginal placenta was diagnosed as not pl praevia by scintigraphy (2 false negative) In 5 o of normal placenta the scintigrams were interp as complete placenta praevia in one case and m nal placenta in 4 cases (5 false positive) The re ing 41 cases were all correctly diagnosed as nor

In the two false negative and the five false po cases the fundus and the symphysis pubis marked by means of a small radioactive so

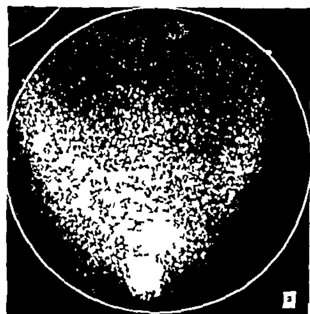
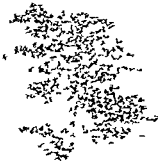




Fig 2 A 25 year-old pregnant woman submitted because of vaginal bleeding Meyer s ring is used for marking (*a*) Anterior view Most of the activity is located low in the pelvis (*b*) Left view Accumulation is seen lo anteriorly Caesarean section three weeks graphy revealed a complete placenta praevia



3 A 27 year-old woman in the 37th week of gestation
is case the symphysis pubis was marked Left lateral
shows accumulation low in the pelvis Above and
riorly is a round area with less activity indicating the
of the fetus Sixteen days after scintigraphy
arean section was carried out A boy lying in trans
position with the head to the left was delivered and a
plete placenta previa was removed

n the radioactive ring round the cervix was the scintigrams were correctly interpreted in cases compared with the final diagnosis

some eases ^{113m}In scintigraphy gave unexpected rmation about the fetus Fig 3 illustrates such a

DISCUSSION

The results of this study confirm that ^{113m}In scintigraphy may visualize the placenta correctly as reported by other authors (2 3 4 5) However there were 7 mistakes in the isotopic localization of the placenta In these cases the fundus and the symphysis pubis were marked by means of a small radioactive source so that the relation of the placenta to the internal cervical os was difficult to interpret When a radioactive ring was used to indicate the cervix all the scintigraphic diagnoses of placenta which were checked were correct Therefore we recommend this new technique in order to facilitate the evaluation of scintigrams

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INFLUENCE OF AGING UPON THE URINARY HORMONE EXCRETION IN THE MALE

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tract The urinary excretion of LH low polar trogens neutral C and C_{21} steroids was measured in mal healthy males aged 20–79 years No significant nges could be noted for the excretion of LH preg ediol and 17 ketogenic steroid between 50 and 79 rs The excretion of androsterone and aeticholanolone significantly lower in the oldest group (70–79 years) A ificant drop in the excretion of DHA was noted at rox 60 years The excretion of low polar oestrogens ained constant from 0 to 55–59 years but showed a dly significant ($P<0.001$) decrease at about 60 years s drop might reflect a sudden decrease in the plasma ls of oestrone sulphate due to a decreased sulphuryl g activity in the liver

production metabolism and excretion of tral steroids in normal males has been exten ly studied and usually there is a fair good correla between blood levels and urinary excretion ies On the other hand the oestrogens in males been considerably less studied One main on for this might be the difficulties involved in measurement of low levels of oestrogens in ogical fluids Most methods used for routine ary oestrogen determinations are neither ific nor sensitive to be applied to urine from nal males Routine estimations of oestrogens in d were not available until recently but the duction of radioimmuno assay and competitive ein binding had caused a dramatic change in this ect

onflicting results have been presented about the ence of aging upon the urinary excretion and the d levels of oestrogens in the male A few studies been carried out and their results are sum zed in Tables I and II While Behrsohn & fse (5) found an increased urinary excretion of oestrone oestradiol 17β and oestriol Pincus (28) found a slight continuous decrease in the excretion of oestrone+oestradiol 17β and an almost constant excretion of oestriol It should be mentioned that the results of Pincus were in agreement with those of an earlier bioassay investigation carried out by that author (27) Kaufmann (22) noted no significant change in the excretion of oestrone and oestradiol 17β The studies on blood hitherto reported indicate increased levels of unconjugated oestrone and oestradiol 17β with increasing age (15 25 31)

As one part of a study on the influence of aging upon the production and metabolism of steroid hormones in the male we have measured the urinary excretion of low polar oestrogens (oestrone+ oestradiol 17β) neutral C_{19} and C_{21} steroids and LH in normal healthy males aged 0–79 years One part of the results dealing with the low polar oestrogen excretion has been presented in a previous communication (35)

ABBREVIATIONS AND TRIVIAL NAMES

Aetiocholanone 3α hydroxy 5β-androstan 17-one Androsterone 3α hydroxy 5α-androstan 17-one DHA 3β-hydroxy 5 androsten 17-one DHA sulphate 3β-sulphoxy 5 androsten 17-one epiandrosterone 3β hydroxy 5α androstan 17-one LH luteinizing hormone (synonym ICSH) oestradiol 17β 1 3 5 (10)-oestratriene 3 17β-diol oestriol 1 3 5 (10)-oestratriene 3 16α 17β-triol Oestrone 3 hydroxy 1 3 5 (10)-oestratrien 17-one oestrone sulphate 3 sulphoxy 1 3 5 (10)-oestratrien 17-one pregnanediol 5β-pregnane 3α 20α-diol testosterone 17β-hydroxy-4-androsten 3-one

Table I *Results from various studies on the age dependence of the urinary excretion of co... oestrogens in normal males*

Age (y)	*n*	Urinary excretion in μg/24 h mean (range) Oestrone	Oestradiol 17β	Oestrone + oestradiol 17β	Oestriol	Ref
20–48	21	4 3 (1 7–9 8)	1 1 (0–3 1)	5 4	2 6 (0 6–9 9)	5
45–65	20	6 3 (2 8–12 5)	2 1 (0 5–3 8)	8 4	6 0 (1 3–1?7)	5
25–39	45			3 48	4 77	[illegible]
40–44	83			3 12	4 78	[illegible]
45–49	101			2 84	4 19	[illegible]
50–59	56			2 63	4 46	[illegible]
60–71	23			1 98	4 13	[illegible]
21–?5	8	7 41	3 52	10 93		[illegible]
26–30	9	6 59	3 44	10 03		[illegible]
31–35	7	5 48	4 08	9 56		[illegible]
36–40	4	4 07	2 75	6 8?		[illegible]
41–50	15	6 52	4 01	10 53		[illegible]
51–60	18	4 59	2 94	7.53		[illegible]
61–70	11	5 52	3 30	8 82		[illegible]
71–83	6	5 49	3 38	8 87		[illegible]

MATERIAL

The younger groups consisted of 41 healthy males aged 20–49 years Most of them were fathers of newly born babies delivered at our Department and the others had normal spermiograms The older groups consisted of 61 healthy men aged 50–79 years They had been admitted to hospital for minor operations predominantly for hernia and varices There was no evidence of endocrinological disorder or abnormalities in the prostate in any case Val es for haemoglobin Na K sedimentation rate uri ry residual nitrogen and urinary sediment were normal nd all patients were free from medications 24 hour urine samples were collected preoperatively

METHODS

LH was determined by the radioimmunosorbent technique of Wide and co workers (39 40) and was expressed as IU of the 2 nd International Reference HMG preparation/24h

Table II *Results from various studies on the age dependence of the plasma levels of unconjugated oestrogens in normal males*

Age (y)	*n*	Mean plasma levels in pg/ml Oestrone	Oestradiol 17β	Ref
22–61	50		16 6	15
67–90	34		25 6	15
21–40	_0	30 1	26 5	25
70–80	10	43 0	21 8	25
<50	30	43	14	31
>65	30	5?	21	31

Low polar oestrogens were determined by the meth... Carlstrom & Furuhjelm (13) Fractionated 11-deo... ketosteroids (DHA androsterone and aetiochola... and pregnanediol were determined by a combination... methods of Carlstrom et al and Carlstrom & Fu... (11 12) 17 ketogenic steroids were assayed a... Birke et al (6) and total 17 ketosteroids by the me... Vestergaard (38)

RESULTS

The results are given in Tables III and IV Th... no significant change in the excretion of ... although the mean value for the oldest grou... higher than for the two other groups Low p... oestrogen excretion was constant from 20 to 5... years At about 60 years this excretion was ab... decreased with about 40% (highly sig... $p<0\ 001$) The excretion of DHA decreased p... ably significantly ($p<0\ 1$) at about 60 years... values for androsterone aetiocholanolo... fractionated 11 deoxy 17 ketosteroids and to... ketosteroids were probably significantly de... in the oldest group ($p<0\ 1$) No significant ... were noted for 17 ketogenic steroids a... nanediol although the mean values f... nanediol were lower in the two older groups

DISCUSSION

No significant age-dependent change in the ... excretion of LH was found in the present st...

ble III *Influence of aging upon the urinary ex tion of conjugated low polar oestrogens estrone+oestradiol 17β) in normal males*

e)	n	Low polar oestrogens μg/?4 hrs Mean	Range
?9	0	5 2±0 4	3–8
39	16	5 0±0 4	3–7
49	5	4 6±0 3	?–7
59	24	5 4±0 5	2–11
69	26	3 3±0 3	1–7
79	13	3 1±0 4	1–6

n agreement with the results of Wide and co- rkers (40) However an age-dependent increase he LH levels has been reported by other workers 31–34)

ndrosterone and aetiocholanolone are mainly reted as glucosiduronates (for a review see 7) age-dependent decrease in the urinary excretion hese steroids has previously been demonstrated other workers (4 28) The age-course of the iary excretion of androsterone+aetiochol lone is similar to that of the urinary excretion onjugated testosterone and to the plasma levels inconjugated testosterone (36 37) Approxi ely 50% of the urinary androsterone and aetio lanolone has been shown to be derived from icular precursors (21)

he main part of the urinary DHA in the male is of al origin although a certain testicular produc f this steroid can not be excluded (21) In the plasma as well as in urine DHA is present almost exclusively as its sulphate (7) In this present study a probably significant decrease in the urinary excre tion of DHA was noted at about 60 years which is in agreement with previous findings by other authors (4 28) A similar decrease in the plasma levels of DHA sulphate was demonstrated by Vihko (41) Vihko found that plasma levels of the sulphates of androsterone epiandrosterone 5 pregnene 3β 20α diol and DHA decreased abruptly at about 60 years in males and about ten years earlier in females Thus the urinary excretion of DHA seems to reflect the plasma levels of this steroid quite well

The excretion values obtained for pregnanediol were close to the specificity limit of the method used and the results should therefore be interpreted con servatively Romanoff and co workers (30) have re ported an age-dependent decrease in the urinary pregnanediol excretion in males In the present study the mean values for pregnanediol were lower in the two older groups but this difference was not statistically significant It should be mentioned that Adlercreutz and co workers (2) found a close corre lation between the urinary excretion of DHA and pregnanediol during normal menstrual cycles They concluded that the excretion of these two uri nary steroids might reflect the production of 3β hydroxy 5 pregnen 20-one which is a proximate precursor to DHA as well as to progesterone/preg nanediol

The excretion of low polar oestrogens in the pres ent series remained constant from 20 to 55–59 years and thereafter decreased abruptly These findings

: IV *Influence of aging upon the urinary excretion of LH and conjugated neutral C_{19} and C_{21} steroids rmal males*

idrosterone E=aetiocholanalone 5α/5β ratio=ratio androsterone/aetiocholanolone 17 KS=17 ketosteroids 17 =17 ketogenic steroids P diol=pregnanediol

	50–59 years Mean	Range	n	60–69 years Mean	Range	n	70–79 years Mean	Range	n
IU/?4 hrs	38±3	17–63	18	37±4	8–74	24	48±7	?1–95	10
mg/?4 hrs	0 39±0 14	0 05–? 40	2?	0 11±0 03	0 05–0 70	?6	0 11±0 03	0 05–0 30	13
g/?4 hrs	2 15±0 27	0 7–5 9	2?	1 91±0 17	0 9–4 1	26	1 8±0 17	0.3–2 8	13
g/?4 hrs	1.58±0 18	0 5–3 4	22	1 3?±0 1?	0 4–3 4	6	1 05±0 21	0.3–? 9	13
ratio	1 47±0 12	0 55–? 84	22	1 85±0 2?	0 59–5 00	6	1 66±0 ?6	0 74–4 00	13
of DHA A and E ?4 hrs	4 08±0 5?	1 4–11 3	22	3 30±0 28	1 3–7 5	?6	? 17±0 46	0 4–6 0	13
17 KS mg/24 hrs	6 ?5±0 54	3 1–10 7	0	6 13±0 43	2 7–13 0	?6	4 77±0 41	2 9–8 1	13
GS mg/24 hrs	8 45±0 76	3 5–15 9	19	8 0?±0 70	3 8–16 2	26	7 37±0 87	3 6–13 1	13
mg/?4 hrs	0 21±0 04	0 05–0 60	19	0 14±0 03	0 05–0 60	?6	0 14±0 04	0 05–0 40	1?

support the results of Pincus (27 28) but are not consistent with those presented by Behrsohn & Oelefse and by Kaufmann (5 22) The results of the later authors might have been influenced by methodological factors since the excretion values presented are about twice as high as those given by Pincus and from the present study

From several studies it is known that approximately 80% of the low polar oestrogen fraction in male urine consists of oestrone (5 8 16 20 24 29) The sulphoconjugate of oestrone is indeed the most abundant low polar oestrogen in peripheral plasma as well as in the bile from males as well as from pregnant and non pregnant females (1 9 14 19 23) As far as we know from the literature no simultaneous assays of conjugated oestrogens in male urine and plasma have been carried out but it is known from studies on pregnant women that the urinary excretion reflects the plasma levels quite well (18) It might therefore be assumed that the drop in low polar oestrogen excretion at about 60 years might reflect a sudden decrease in plasma oestrone sulphate which in turn coincides with the previously demonstrated drop in plasma neutral steroid sulphate levels (41)

Vermeulen and co-workers (37) have recently studied the urinary excretion pattern of the metabolites of injected radioactive testosterone in young (25–50 years) and old (>68 years) males They found the transformation into glucosiduronates remained constant and independent of age while the amount of sulpho-conjugated metabolites formed in the older group was only about 40% of that in the younger group The decrease in urine and plasma values for steroid sulphates might therefore be attributed to a decrease in the sulphurylating activity in the liver It has recently been demonstrated by Carlstedt Duke & Gustafsson (10) and by Eriksson (17) that *in vivo* administration of androgens to rats decreased the *in vitro* steroid sulphurylating activity in the liver while oestrogens increased this activity It is therefore tempting to speculate over a regulatory effect of sex steroids on the sulphurylating activity in man Thus it might be possible that an agedependent drop in the oestrogen production causes a decrease in the liver sulphurylating activity

A decreased sulphurylating of oestrone might lead to increased levels of unconjugated oestrone and oestradiol 17β in plasma and this might explain the increased plasma levels of unconjugated oestrogens found in older males (15 25 31) Oestradiol [is] generally considered as the most potent n[atural] oestrogen and thus the increased levels of [this] steroid might at first speak against an oe[strogen] dependent decrease in sulphurylating act[ivity] However it should be kept in mind that the pla[sma] levels of unconjugated oestrogens in males are approximately one tenth to one fifth of the oes[trone] sulphate levels (19 23) Oestrone sulphate might excert considerable biological effects a[fter] after its hydrolysis in the target organs (for a re[view] on this subject see Adlercreutz (3)) Further[more] the plasma levels of unconjugated oestrogens [in] older males might be strongly influenced by [de]creased metabolic clearance rate and incre[ased] levels of steroid binding proteins (31 34) Th[e] estimation of unconjugated oestrogens in pla[sma] might not give a true picture of the total oes[trogen] production in the male We are therefore repea[ting] this investigation using radioimmunoassay [of] oestrone sulphate in plasma and the results are [to be] published later

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LUMBAR EPIDURAL ANALGESIA IN LABOUR

A Clinical Analysis

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tract Lumbar epidural block was given for pain relief '96 women in labour Bupivacaine was used as the lgesic agent and the technique is described in detail sfactory analgesia was obtained in 92% of the cases ng the first stage of labour and in 84% during the ond stage of labour *The frequency of instrumental* veries and of occipito-posterior position increased but clinical condition of the newborn seemed to be unaf ed

tinuous *lumbar epidural analgesia in labour* bupivacaine as the local analgesic agent has used since 1969 at the Department of Obstet and Gynæcology Karolinska Hospital Stock This retrospective survey of 296 deliveries *r epidural block was done to summarize our* cal experience with this type of analgesia

idural block during labour has been used for y years on the North American continent but as ice varies in different countries the experi of *others cannot always be transferred* This should be seen as a survey of epidural block g labour in a Swedish Hospital

MATERIAL AND METHODS

nts

period July 1969 to March 1963 a total of 296 women f all vaginal deliveries) were given an epidural block labour at the Department of Obstetrics Karolinska tal Their age ranged between 15 and 38 years 25 years) 252 were nulliparae and 44 multiparae thers had uncomplicated pregnancies and all babies ingleton and born as vertex presentations

ions

al block was mainly given when unsatisfactory sia was obtained with conventional methods line and nitrous-oxide) Occasionally the indication for this type of analgesia was an unusual fear of labour pains and in these cases labour was often induced and the patient was given an epidural block as soon as she had regular contractions In patients with incoordinated uter ine action the epidural block was performed both to reg *ularize contractions and to alleviate pain* (7)

Contraindications

Epidural block was not given to patients with central nervous system diseases allergy to local analgesic agents and infections of the lumbar skin area Patients with coagulation disorders were also excluded

Borderline pelvis as evaluated by X ray pelvimetry breech presentation and multiple pregnancies were con sidered as obstetrical contraindications to epidural block

Technique

The epidural space was entered with an 18 gauge Tuohy needle in the second or occasionally third lumbar inter space A midline approach with the loss of resistance technique was used and a catheter was inserted through the needle for 4–5 cm in a cranial direction The external portion of the catheter was secured to the patient s back with adhesive tape and the distal end connected to a bacterial filter (Millipore®) through which all injections were made Aspiration through the catheter was done in all cases before injection of the test dose In eight cases no catheter was used and only one single injection was given due to the late stage of labour

In cases of unsatisfactory analgesia a more con centrated analgesic solution was used and if the patient was still uncomfortable the epidural catheter was re

Table I *Analgesia during the first and second stage of labour after epidural blockade*

Labour	Satisfactory analgesia (%)	Unsatisfactory analgesia (%)
First stage	92	8
Second stage	84	16

Table II *Lumbar epidural analgesia in labour all cases Frequency of spontaneous deliveries instrumental deliveries and caesarean sections*

		Normal delivery		Instrumental delivery		Caesarean section	
	No	No	%	No	%	No	%
Nulliparae	252	130	51 6	106	42 1	16	6 3
Multiparae	44	37	84 1	6	13 6	1	2 3
Total	296	167	56 4	112	37 8	17	5 8

positioned Reposition of the catheter was done in 12 cases

The maternal blood pressure was recorded with a cuff manometer every 5–10 minutes during the first 30 minutes after each injection and then every 15 minutes Hypotension was defined as a fall in systolic blood pressure to a level below 100 mmHg In all cases an intravenous cannula was inserted and 500–1 500 ml of 5% glucose was infused throughout labour In the last hundred cases the infusion was started 10–15 minutes before analgesia and 500 ml of fluid was rapidly infused to counteract blood pressure falls

Drug dosage

Bupivacaine 0 25% with adrenaline 1/200 000 (Marcaine Adrenaline®) was used as analgesic agent and administered at demand about every second hour in doses of 6–8 ml after an initial test dose of 2 ml In 53 cases a 0 5% solution was used to achieve adequate analgesia The mean total dose given was 44 mg (range 15–192 mg) and the mean number of injections given to each patient was 2 5 (range 1–9)

ntrol of patients

The epidural block was started when the patient was in need of pain relief had regular contractions and the cervix was open for more than 2–3 cm

Before analgesia was given the obstetrician evaluated the bituberous diameter and checked that the fetal head was fixed in the pelvic inlet X ray pelvimetry was performed in all cases with uncertain pelvic capacity If the membranes had not ruptured spontaneously amniotomy was performed at a cervical dilatation of 4–5 cm The degree of bladder distension was checked regularly throughout labour Instrumental delivery was performed in all cases when the presenting part had been on the pelvic floor for more than 60 minutes

The fetal heart rate (FHR) was recorded by direct auscultation every 15 minutes during the first stage and every 3–5 minutes during the second stage of labour In 61 cases a cardiotocograph (Hewlett Packard no 8020 A) was used for continuous recording of FHR and uterine contractions

Evaluation of the analgesic effect

The analgesic effect of the blockade was evaluated by the anaesthetist during the first and second stage of labour and registered on a protocol The analgesia wa *satisfactory* when the patient did not co seemed to be pain free and comfortable All were judged as *unsatisfactory*

RESULT

Analgesic effect

In 24 cases (8%) the analgesia was judg *satisfactory* during the first as well as t stage of labour (Table I) In two further ca were excluded from the total series th space could not be localized and no blo performed In 46 cases (16 per cent) the was *satisfactory* during the first stage of l *unsatisfactory* during the second stage (Table I) In 23 of these cases a puden (10+10 ml 1% Prilocaine) was given for d

Complications

A dural puncture occurred in 3 cases I these cases this complication was recog fore the anaesthetic solution was inje an epidural block was performed withou cations through another lumbar interspace

In the third case the puncture of the discovered after the injection of 2+8 ml bupivacaine adrenaline The patient w year old nullipara with a normal pregnanc tinuous lumbar epidural block was perf cause of painful and incoordinated uteri tions No abnormalities were recorded aft *dose of 2 ml but less than one minute* injection of 8 ml 0 25% bupivacaine adre pain disappeared and the patient s systol pressure fell to 75–80 mmHg The FHR by stethoscope) which previously had b mal fell to about 80 beats/minute and th level of the anaesthesia reached Th IV blood pressure returned to normal wi with i v fluids and lateral positioning of the

Table III *Indications for instrumen al de ter epidural block in labour*

	No	Fetal asphyxia	Uterine inertia	Co
Nulliparae	106	25	80	1
Multiparae	6	1	5	0
Total	112	26	85	1

le IV *Indications for caesarean section after epidural block in labour*

	No	Fetal asphyxia	Threatened rupture of the uterus	Narrow pelvis	Uterine inertia
parae	16	9	2	4	1
parae	1	1	0	0	0
l	17	10	2	4	1

fter a short period of moderate fetal tachy lia a new episode of accentuated FHR lycardia was recorded and a caesarean section performed for impending fetal distress The / scored Apgar 9 at one minute A couple of after the operation the patient complained of re post spinal headache

3 cases the anaesthetic solution was probably ted directly into an epidural vein The patients ted with hypertension tachycardia pallor and essness for a couple of minutes after the injec of 2+8 ml 0 25% bupivacaine adrenaline but without symptoms after about 5 minutes Af he catheter had been repositioned adequate esia was obtained

systolic blood pressure below 100 mmHg was rded in 30 patients mostly after the first ural injection but occasionally after reinjection patients were treated in a lateral position and rapid i v infusion of fluids In two patients 25 of ephedrine was given i v in addition to this ment The blood pressure returned to normal lly in all cases

our and delivery

umental delivery by vacuum extraction was ed in 37 8% of the cases Instrumental delivery was less frequent in nulliparae than multiparae (Table II) The indications for instrumental delivery are given in Table III During the same period the frequency of instrumental deliveries at this department was 8 3% Patients with epidural block and caesarean section excluded

Caesarean section was performed in 17 cases (Table II) which represents 5 8% The indications are given in Table IV

Nine per cent of the babies were born in occipito-posterior position (Table V) and corresponding figures in patients without epidural block was 3 4% during the same time period

Oxytocin stimulation was used in 122 patients before as well as after the epidural block and in 55 patients after the blockade

The time interval between the induction of analgesia and delivery was four hours seven minutes (range 24 hours 44 minutes—20 minutes)

Clinical condition of the newborn

The Apgar scores of the newborn at birth and after 5 and 10 minutes are given in Table VI There were two cases of stillbirth one case of hydrops fetalis due to Rh incompatibility and one case of hydrocephalus which was perforated during labour Two further babies had multiple malformations

V *Frequency of occipito posterior and occipito anterior position at delivery after epidural ade for labour*

	Normal delivery	Occipito posterior No	Occipito posterior %	Occipito anterior No	Occipito anterior %
arae	236	21	8 9	215	91 1
arae	43	4	9 3	39	90 7
	279	25	9 0	254	91 0

86

Table VI *Apgar score of the newborn after delivery with epidural block*

Apgar score	At birth No	At birth %	5 minutes No	5 minutes %	10 minutes No	10 minutes %
8–10	271	91 5	289	97 6	292	98 6
5– 7	20	6 8	5	1 7	2	0 7
0– 4	5	1 7	2	0 7	2	0 7
Total	96	–	296	–	296	–

Stillbirths (congenital malformations)

which required emergency surgery Both died within one week after delivery All the other children were discharged in good health from the hospital

DISCUSSION

Lumbar epidural block provides an effective pain relief during the first stage of labour and is a well *documented technique (4 5 6) Bupivacaine* a long acting agent was used as the local analgesic in this study From a pharmacological point of view bupivacaine seems to have certain advantages in obstetrics (2 3 11 12) and the relatively long time interval between each epidural injection is in our *opinion an advantage when pain relief is needed for* a long period

Bupivacaine with adrenaline was used in this study *mainly* because *adrenaline free* solutions were not available when this investigation was started The addition of adrenaline does not seem to prolong the analgesic action of the drug but a certain reduction of the blood concentration can be seen and in cases requiring a prolonged analgesia the addition of adrenaline could be beneficial (13)

In this study the success rate was over 90% in the first stage of labour which is in agreement with other studies (6 9) *Pain relief* was less *effective* during the second stage of labour This is probably due to the technique used with small volumes of bupivacaine to minimize pelvic floor relaxation and preserve the bearing down reflex A higher success rate during the second stage of labour can probably be achieved with larger volumes and more concentrated drug solutions This would however probably increase the frequency of instrumental deliveries

The suture of an episiotomy or the exploration of the uterine cavity post partum can easily be done after a top up injection of bupivacaine

Dural puncture and inadvertent intravenous injection of the local anaesthetic agent are known complications of this technique (8) When these types of complications are properly diagnosed and treated no permanent damage to mother or child should occur but constant supervision of the patient is *essential In this study one case of unre*cognized high spinal anaesthesia occurred which is a potentially dangerous complication when not properly treated The test dose of 2 ml used is probably too small and is no guarantee against an intravenous subdural injection of larger vo the local anaesthetic agent

The incidence of hypotension is simil found in other investigations (5 7) Lateral p ing of the patient and intravenous fluids is a tive treatment in the majority of the cas hypotension is no major problem with th nique Diagnosis and treatment of this co tion should however be adequate to avo *compromise*

After an epidural block the mother will be conscious of uterine hyper or hypo Control of labour should therefore be very and cardiotocography is probably the best supervising mother and child In this stu *cases of threatened rupture* of the uterus which definitely stresses the importance of tive control of the patients Borderline *evaluated by X ray pelvimetry is in our* relative contraindication to epidural block cin stimulation of labour is probably more after epidural block which also emphasises of adequate supervision

An increased frequency of instrumen liveries will occur after epidural block phenomenon is probably mainly due to th gesia of the perineum with a decreased down reflex It is therefore important that and midwifes are properly instructed Be the decreased bearing down reflex se epidural block breech position and mult nancies represent in our opinion a rela traindication to this type of analgesia

The reason for the increased frequ occipito-posterior position after epidural difficult to evaluate Rotation of the fetal hea be disturbed by the pelvic floor relaxation epidural block (4) but on the other hand occipito-posterior position may in itself rather painful labour and these cases could represented in this series

Apgar scores were within normal epidural block and the frequency of babies was similar to that found in the partment and during the same period af tional obstetrical analgesia (1) In view of *parent lack of neonatal depression* (10 14 few complications encountered continuo block with bupivacaine is in our opi method when effective pain relief is labour

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FETAL MOVEMENTS DIAGNOSED BY ULTRASOUND IN EARLY PREGNANCY

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stract The purpose of this work was to ascertain ether ultrasonic techniques based on fetal movements re suitable for examinations in early pregnancy The ies consisted of 174 patients who came to be examined cause of bleeding on the 6th–20th gestational week The nd B scan method detected the fetal movements from 8th week onwards and the results were 100% reliable m the 10th week onwards The combined A–B scan thod detected the fetal movements from the 12th week chniques based on the detection of fetal heart function re used as control methods According to our results methods based on the indication of fetal movements istitute a practical alternative for elucidating the prob is of early pregnancy

ring the last few years ultrasonic examination established its position in the diagnosis of early gnancy and its complications By means of the can method intrauterine pregnancy can be de ted from the 6th gestational week onwards This thod can also be used to measure the growth of gestation sac and the uterus in early pregnancy t the use of the B scan technique which is the st advanced ultrasonic method is restricted in ly pregnancy by the fact that it does not show ctly whether the fetus is alive or not Attempts e therefore been made during recent years to elop new ultrasonic methods or to combine ex ng ones in such a way as to show fetal heart ction (5 6 7 11) These methods are however ier relatively elaborate ultrasonic techniques or nbinations of several methods and hence re re considerable experience of the examiner n addition to displaying fetal heart function fetal can also be verified in early pregnancy by de tecting fetal movements This can be done by two ultrasonic methods One of these is the combined A–B scan in which an ultrasonic beam is di rected towards the fetus on the basis of the informa tion shown by the oscilloscope of the B scan ap paratus and the movements of the fetal echoes on the A-oscilloscope then show the fetal movements The other technique is based on the rapid B scan method [1] whereby fetal movements are directly observable on the oscilloscope of the apparatus In order to find out whether the mere diagnosis of fetal movements in early pregnancy can lead to a suffi ciently early verification of fetal life we compared the ultrasonic techniques showing fetal movements with those used to display fetal heart function

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[1] erms "split image technique and rapid picture nation are also used

MATERIAL AND METHODS

The patient series consisted of 174 patients admitted into the Department of Obstetrics and Gynecology University of Oulu on the 6th–20th gestational week because of bleeding

In each case a rapid B scan was obtained first using the Vidoson® (Siemens) apparatus (Fig 1) In this apparatus a rotating probe transmitting and receiving ultrasound (2 MHz) gives two-dimensional cross section images of the object on the oscilloscope at such high frequency (16/sec) that spontaneous fetal movements can be demonstrated The liquid filled probe of the apparatus can be placed in different positions above the object Oil was used as a contact medium between the probe and the skin and the full bladder technique was employed to localize the uterus The first objective was to detect fetal echoes in the uterus After this had been done their possible movements were followed for 5 minutes when necessary (Figs 2 and 3) In the other method of verifying fetal movements the combined A–B scan method (Kretztecknik s 4100 MGS apparatus) was used (Fig 4) A 2 MHz ultrasound was directed towards the fetus on the basis of the information shown on the B scan oscilloscope The fetal echoes were

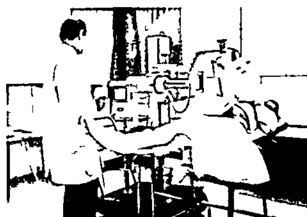


Fig. 1 Equipment (Vidoson®) based on the rapid B scan method The liquid filled probe on the patients abdomen

then seen as vertical echo peaks on the A-oscilloscope of the same apparatus (Fig 5) The rapid horizontal shifts of these echoes were taken as signs of fetal movements

Three control methods showing fetal heart function were used The first of these was the combined A-B scan with Kretztecknik s 4100 MGS apparatus and a 2 MHz probe whereby after the initial information obtained from the B scan the detection of the fetal heart function

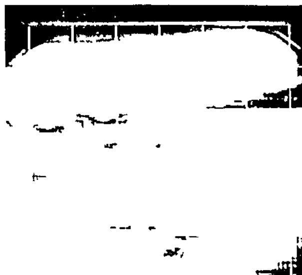


Fig. 2 Longitudinal rapid B scan of the uterus in the 9th week The examination is based on the possible movements of fetal echoes (*F*) on the oscilloscope *Bl* = bladder *GS* = gestation sac

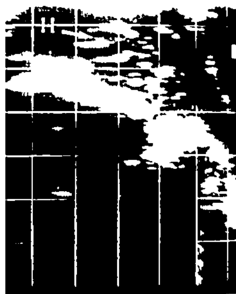


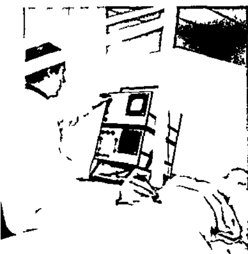
Fig. 3 Longitudinal rapid B-scan in the 14 h we echoes of fetal head (*H*) can be seen in the *Bl* = bladder

was possible as a typical rotating movement i A-oscilloscope (Fig 6) The other methods incl nal Doppler examination by means of Picker s apparatus and a 5 MHz probe (5) and a combine and Doppler examination with Kretztecknik s 4 apparatus supplemented by Picker s EUD-I cur carried out transabdominally by a 5 MHz probe

If one of the methods employed showed the fe alive on the first examination no further sca made In the other cases examinations were intervals of 1–2 weeks until fetal life was pregnancy terminated spontaneously From the onwards however no repeated examinations Two examinations were made in altogether I three examinations in 8 cases Molar and nancies were excluded from the series The of the patients were further followed by tion quantitative daily urine HCG assays and of the subsequent course of the pregnancy

RESULTS

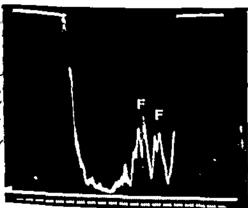
In the series investigated (124 patients ultrasonic examinations and subsequent f showed continuation of the pregnancy in 1 (57 2%) In the remaining 53 cases (4 pregnancy terminated in a spontaneous abo



f Combined A–B ultrasound equipment (Kretztech 100 MGS) Longitudinal examination

these cases the diagnosis was missed abortion uterine evacuation revealed a dead fetus on the 19th week of pregnancy In 3 cases out of e 7 signs of fetal life had previously been de strated by ultrasound The size of the fetus ested however that death had taken place af he scan In the other cases which terminated in ntaneous abortion no signs of fetal life had been aled by ultrasound Most of them turned out to ases of blighted ova

he results obtained with the present ultrasonic nods are shown in Table I The rapid B scan aled the first fetal movements in the 8th gesta



5 Fetal echoes (F) on the A-oscilloscope The rapid ontal movements of the echoes indicates the fetal

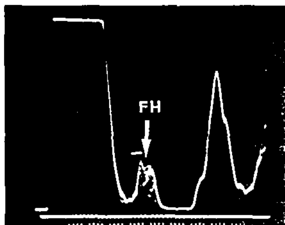


Fig 6 Fetal heart action (FH) on the A-oscilloscope Echoes of fetal heart seen as a typical rotating movement

tional week in 3 cases From the 10th week on wards the results were 100% correctly positive or correctly negative No false positive findings were obtained This method showed the fetal movements to be slight on the 8th–9th gestational week and their detection often required a long time It was also relatively difficult to see the fetal echoes in the gestation sac at this time From the 10th week on wards the intensity of fetal echoes the frequency of movements and the duration of each series of movements clearly increased until the end of the period of investigation Though the fetal move ments were not analyzed in any more detail two types of movement could be distinguished The first type included violent movements of the whole fetus which changed entirely its position in the amniotic cavity The other type consisted of smaller movements probably of the limbs after which the fetus retained its previous position in the amniotic cavity *The period of immobility between move* ments was shorter in the first type In the cases where no movements in the uterus could be de tected the oscilloscope showed whether the case was one of intrauterine pregnancy whether the size of the gestation sac was equivalent to the duration of pregnancy or smaller and whether fetal echoes were detectable in the gestation sac or whether the sac was empty

Fetal movements were detected later by the combined A–B scan method than by the rapid B scan The first movements of fetal echoes were observable in the 10th gestational week and full reliability was only achieved from the 12th week

Table I *The percentages of correctly positive and correctly negative findings from the total [illegible] examinations (N) made by ultrasonic methods to show fetal life in the 6th–20th gestational week [illegible] patients with symptoms of threatened abortion (153 examinations)*

Ultrasonic method	Gestational weeks 6th N=5	7th 9	8th 16	9th 18	10th 29	11th 32	12th 21	13th–20th 23
Rapid B scan	0	0	19	50	100	100	100	100
Combined A–B scan	0	0	0	0	24	72	100	100
Methods based on the detection of fetal heart function	0	12	75	94	100	100	100	100

Used to detection of fetal movements

onwards (Table I) In this method too the horizontal movements appeared to become the stronger and the more easily discernible the longer was the duration of pregnancy No false positive findings were obtained The B scan oscilloscope further permitted the usual diagnostic observations on the size of the gestation sac and the uterus and on the fetal echoes

The control methods based on the detection of fetal heart function by ultrasound yielded the first positive findings in the 7th gestational week in the same series of patients The findings were almost completely reliable from the 9th week a false negative finding was only obtained in one case out of 18 The findings were 100% correctly positive or correctly negative from the 10th gestational week onwards

DISCUSSION

The present findings showed that ultrasonic methods based on fetal movements indicate fetal life from the 10th gestational week onwards Although the rapid B scan method detected fetal life in the 8th and 9th gestational weeks less often than did the ultrasonic methods based on fetal heart function both techniques yielded 100% diagnostic reliability in the same week (the 10th gestational week) The findings obtained by rapid B scan are also very clear and illustrative The combined A–B scan method revealed fetal movements about two weeks later than rapid B scan One explanation for this might be that ultrasound directed by the former method only to the fetal body may not reveal movements which involve the limbs alone The movements of fetal echoes in positive cases however are clearly interpretable in the A–B scan method and the examiner finds it easy to d[illegible] movements after a few positive findings

The fetal movements diagnosed in the pr[illegible] investigation proved to be similar to those de[illegible] previously by Reinold with the rapid B scan [illegible] (8 9 10) Our own experience is limited [illegible] exclusively to abnormal pregnancies and [illegible] fore know little of the fetal movements in [illegible] early pregnancy Reinold (9) showed however [illegible] restricted spontaneous fetal motility in the [illegible] results in the birth of a healthy infant in only [illegible] the cases while the prognosis for infants [illegible] mal fetal motility is good in 94% He [illegible] demonstrated that absence of fetal response [illegible] trauterine manipulation signifies a poor pr[illegible] for the fetus even if signs of life were visible [illegible] time of the examination According to Re[illegible] the observation period must last for at least [illegible] utes Haller et al (3) who employed th[illegible] ultrasonic technique were able to show th[illegible] frequency and duration of fetal movements [illegible] significantly reduced in pregnancies subse[illegible] terminating in an abortion than in cases [illegible] favourable prognosis It is hence possible th[illegible] rapid B scan method may give prognost[illegible] tion for the subsequent course of the preg[illegible]

The diagnosis of fetal movements by the [illegible] described above is a new advance in the [illegible] early pregnancy It has been shown previous[illegible] fetal movements begin at a very early sta[illegible] lepiane (1) demonstrated fetal movement[illegible] age of 8 weeks in a gestation sac remove[illegible] from a tubal pregnancy Muscular co[illegible] have been observed in fetuses 6 weeks o[illegible] Szendi (12) demonstrated fetal moveme[illegible] gestation sac during the first four mo[illegible] trast medium and X rays The ultraso[illegible]

ployed in the present work did not reveal fetal ements until the 8th gestational week because etal echoes could be seen prior to this time The ustic properties of the fetal tissues at an early e differ so little from the surrounding amniotic l that the detection of the fetal echoes requires icularly sensitive equipment (11)

he ultrasonic research into early pregnancy car l out during the last few years has focussed in asingly on the demonstration of signs of fetal The main reason for this has been the fact that n the B scan method alone is used diagnostic ability after a single examination is only 78–87% 4) Absence of fetal heart function from the –10th gestational week onwards on the other d is a certain sign of a poor prognosis for the gnancy (5 7) Robinson (11) achieved complete gnostic reliability from the end of the 7th gesta al week onwards by using a combined B–A–TM hod in the demonstration of fetal heart function the basis of the present results it appears that a nosis of fetal movements leads to 100% nostic reliability in the verification of fetal life iciently early i e from the 10th gestational k onwards The present work also confirmed a vious observation (5) showing that verifiable is of fetal life signify a favourable prognosis for pregnancy despite symptoms of imminent rtion in over 90% of the cases Since more r the findings are perhaps easier to interpret the ultrasonic examinations based on fetal ements than in the other ultrasonic examina s of early pregnancy these methods particu the rapid B scan method can be considered ticable alternatives in the choice of ultrasonic niques for studying early pregnancy As the ings are unambiguous and easy to interpret the hod can also be recommended for examiners have little experience with ultrasound

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CHANGES IN THE CERVICAL BLOOD FLOW DURING LABOUR

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ract The cervical blood flow changes during labour egnant women (15 cases) have been studied by local tion of ³Xe into the cervix The blood flow changes compared with the external uterine pressure which measured with a tocograph During contractions the activity decreased temporarily but increased again een contractions The overall decrease was greater in ontrol group (4 cases) than during spontaneous con ions The conclusion is that relative cervical blood ılation is rapidly changed during labour

blood flow through the uterus and the placenta been studied with different methods The indi al variations in the results are wide and depend ı on the duration of the pregnancy and on its plications

udies with isotopes have provided much useful mation Munck et al (8) first used ¹³³Xenon ical injection to assess the circulation in uterine le (13 ml/100 g/min) With the same technique hem et al (2) observed a progressive decrease enon-clearance as pregnancy progressed Falk (1) studied the effect of the distance of the tion point from the placenta Pontonnier et al observed near the placenta the initial rapid e (?1 0±8 5 ml/100 g/min) and the slow phase ⊦3 1 ml/100 g/min) which was nearly equal to blood flow in the non placental side of the metrium Jansson (4) did not observe any dif ce in the clearance rate between different parts e non pregnant uterine body and it was equal thological and normal pregnancies Laakso et 5) observed with the scintillation camera that erfusion reached a maximum at the 34th week fell to a low level by the 40th week but no rence was found between normal and patholog pregnancies Also Janisch and Leodolter (3) ⁹⁹ᵐTc distinguished three groups of patients ıe basis of the type of flow curve In the first group with the maximal peak the delivery and babies were normal and in the other groups there were pathological findings

We have studied the blood flow in the cervix during labour correlated with regular contractions The results are expressed qualitatively

METHODS AND MATERIALS

The tracer used was ¹³³Xenon The dose was 100 μCi in 0 1 ml saline solution The tracer was injected slowly (15 sec injection period) into the cervix between contractions and the long needle was kept in the muscle for 10–15 seconds after injection The collimator with NaI-crystal was placed over the symphysis

One channel pulse height analyzer recorded the result on a chart

At the same time the uterine pressure was measured with a Hewlett Packard external tocograph

The measuring time was about 15 minutes

The patients included 10 normal pregnant women 5 toxemic women during regular spontaneous contractions and 4 normal pregnant women without contractions

RESULTS

The level of radioactive tracer ¹³³Xe decreased during regular contractions between contractions the radioactivity accumulated again However the changes happened a little after the peak of the con centration and after maximal relaxation (Fig 1) During a contraction the cervix probably became a bloodfree area and afterwards blood and Xenon flowed back

The curves for the 2 women (X and Y) without contractions are illustrated in Fig 2 Comparing the curve during contractions with the one recorded without any contractions we found that the de crease of radioactivity in the last curve was deeper and more rapid

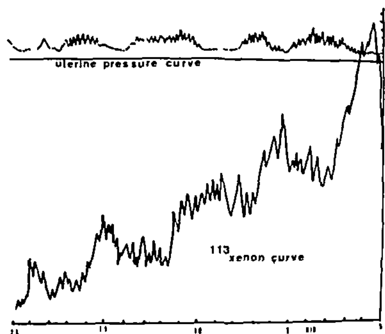


Fig 1 The pregnant woman d... contractions

DISCUSSION

Morris et al (7) and later Payling Wright et al (11) observed by using radioactive sodium that the uterine blood flow decreased both during exercise and labour

Scheffs et al (10) analysed by computer the placental flow curve during labour finding that the blood flow starts to increase during the relaxation phase and continues up to an intrauterine pressure of about 30 mmHg in the next contraction This increase is related to venous compression in the presence of a normal arterial flow Shortly after the peak of a uterine contraction the blood flow again starts to increase Although these measurements were made in the uterine body the same results can be obtained from the cervix The blood flow in the cervix is even higher than in the uterine body whereas the blood pool in the placental side of the uterus is about twice that in the non placental side Radioactivity returns to the cervix between contractions from this pool probably by back flow Some Xenon labelled blood is also lost into the general circulation during a contraction This distribution from the cervix however is slower during contractions than in a patient without contraction according to our figures

The transport of the tracer from the injection point can vary because it is impossible to know the relationship between the injection site and the vessels near which the transport is most r... cause this affects the quantitative measur... the blood flow we have not calculated it a... it is possible to do so by using Lassen's m... for muscle blood flow

These physiological findings are in ... with previous clinical impressions Howev...

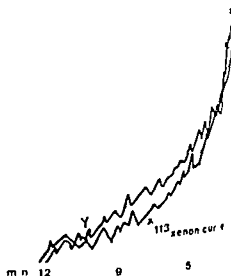


Fig 2 Two pregnant women (X and Y) ... tractions at term

it is possible to follow qualitatively the relationship between external uterine pressure ervical blood flow

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UNCHANGED TOTAL BODY CALCIUM IN NORMAL HUMAN PREGNANCY

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ract The total body calcium—estimated from bone ral content in the distal part of the forearm measured se of photon absorptiometry—was determined during nancy in 13 women The results indicate that total calcium is constant during pregnancy

skeleton of newborn human infants contains ly 25 g calcium and 80% of this amount is ed up in the last trimester of pregnancy (8) litionally pregnancy is considered a state in h calcium is lost from the maternal skeleton ight & Reifenstein (1) postulated that preg y and lactation were factors that cause porosis in women A high incidence of porosis in multiparous women compared with parous has been reported by some investigators 3) Other authors were unable to find this dif ce (6 9)

kinson & West (2) have demonstrated by use of on absorptiometry that lactating women lose t 2% of the total body calcium per 100 days oton absorptiometry of the distal part of the rm is a reasonably good estimate of total body im especially in well defined groups of pa (3 4)

report here a prospective study in pregnant n which aims at an evaluation of a possible e in total body calcium during pregnancy

MATERIAL AND METHODS

en women attending the out patient clinic at the tment of Obstetrics and Gynecology at Glostrup al took part in the study They had all been preg or 3–4 months at the beginning of the investigation of the women has symptoms of renal or digestive Clinical data are given in Table I

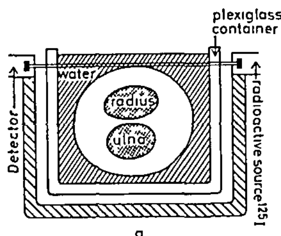
The bone mineral content (BMC) was determined by direct photon absorptiometry on both forearms (Fig 1) The forearm is fixed in a Plexiglass container filled with distilled water The source of radiation (25 mCi ^{125}I) and the detector are fixed in a holder at each side of the bones to be examined A mechanical scanner displaces the de tector and the source perpendicular to the longitudinal axis of the bones The transmission of photons through the bones depends on the bone mineral content Because the linear attenuation coefficients of Plexiglass distilled water and soft tissue are almost identical the measure ment is independent of the amount of soft tissue In our modified version the BMC is expressed in arbitrary units as the mean value of six scans from each forearm BMC of the forearm is well correlated to the body s total calcium content espe ially in normal subjects (4 5)

Initially (at time t) BMC was measured Thereafter the measurements were repeated at time t (at 5–6 months pregnancy) at time t (at 7–8 months pregnancy) and at time t_3 (at 9–10 months pregnancy) After the last meas urement the women were questioned about their extra daily calcium supply during pregnancy (tablets and/or milk) Values for this supply are given in Table I

As BMC is a function of sex and age (4) the BMC values of the pregnant women are expressed as per cent of the corresponding normal mean (Table II) To evaluate a possible change during pregnancy the initial value in each patient was termed 100 per cent and the following BMC values were recalculated to per cent of the initial value (Fig 2)

Table I *Height weight age previous pregnancies and daily calcium supply in 13 pregnant women*

	Mean	Range
Height (cm)	164 2	150–174
Weight at time t (kg)	6? 4	52–86
Age (years)	?6 3	21–35
Previous pregnancies	1 2	0–2
Daily calcium supply (mg)	650	300–1200



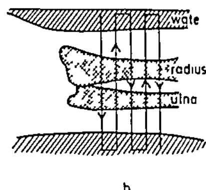


Fig 1 Method of measurement of bone mineral material content by direct photon absorptiometry on forearm (A) Section through system showing Plexiglass container and U shaped holder with radioactive source and detector (B) System seen from volar surface showing the movements of source and detector

RESULTS

In Table II the BMC expressed in per cent of the corresponding normal mean are given as a function of time None of the mean values (at time t_0 t_1 t_2 and t_3) are significantly different from the normal mean (100%) Fig 2 shows the BMC values in per cent of the initial value during the study expressed in this way the BMC did not change

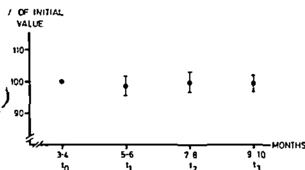


Fig 2 Bone mineral content (BMC) in 13 pregnant women as a function of time (t_0 t_1 t_2 and t_3 corresponds to length of pregnancy of 3–4 5–6 7–8 and 9–10 months respectively) BMC values given as per cent of the initial value Each point represents mean ±1 standard error of mean

DISCUSSION

The present results indicate that women given an extra supply of calcium do not lose calcium from the skeleton during pregnancy Or in other words that women do not develop osteopenia when pregnant A significant fall in BMC of lactating women can be demonstrated only if the lactation period exceeds 3 months (2) As this is the exception rather than the rule in Denmark it seems improbable that pregnancy and lactation are a factor of risk as regards the development of osteoporosis

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Table II *Bone mineral content (BMC) in per cent of corresponding normal mean (x) as a function of time in 13 pregnant women*
Values are given as mean ±1 S E M

	3–4 months (t_0)		5–6 months (t_1)		7–8 months (t_2)		9–10 months	
	Mean	S E M	Mean	S E M	Mean	S E M	Mean	S
$\frac{BMC}{x}$ 100%	10? 1	5 0	99 7	4 3	100 7	3 5	100 9	4

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PHOSPHOLIPIDS AND CREATININE IN AMNIOTIC FLUID IN RELATION TO GESTATIONAL AGE

II *Complicated Pregnancy*

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act 176 samples of amniotic fluid were obtained by minal amniocentesis from 69 women with compli l pregnancies (toxemia diabetes mellitus or rhesus imunization) in the 27th–43rd week of pregnancy concentration of creatinine (172 cases) the ratio ecithin/sphingomyelin (L/S ratio 155 cases) and pholipid phosphorus (155 cases) were determined and ed to gestational age The results were compared with al pregnancy The mean level of *creatinine in tox* was significantly higher from the 32nd week till term 05) and the L/S ratio was significantly higher 05) in the 34th–35th week compared with normal nancy Creatinine concentration was significantly ted in diabetic pregnancy in the 36th–37th week 05) Creatinine *concentration tended to be low in* oimmunization A creatinine concentration ≥1 8 and a L/S ratio ≥2 25 always corresponded to a tional age ≥35th week To get increased precision in ating gestational age in complicated as well as in al pregnancy the determination of both creatinine ntration and *L/S ratio in amniotic fluid is* recom ed

accurate estimation of gestational age and fetal rity is essential prior to elective induction or ive cesarean section and for the evaluation of risk pregnancies such as toxemia Rh iso inization diabetes suspected postmaturity placental insufficiency Current methods for nation of gestational age and *fetal maturity* t fail with serious consequences especially in risk pregnancy In a previous study we found that the determination of the lecithin/sphingo in ratio (L/S ratio) and creatinine concentra in amniotic fluid samples *obtained by amnio* sis could be used for estimation of gestational with good precision

In the present investigation we have determined the lecithin/sphingomyelin ratio (L/S ratio) the concentration of creatinine and phospholipid phos phorus in amniotic fluid in different groups of com plicated pregnancy and have related the results to the gestational age As was the case in normal preg nancy the combined determination of creatinine concentration and L/S ratio made possible the de termination of gestational age with good precision in complicated pregnancy

MATERIAL

The group includes all patients with complicated preg nancy according to Table I who were treated and deliv ered at the University Hospital of Umeå during the period February 1972 until June 1973 Gestational age was estimated according to criteria given earlier (10) Women with uncertain gestational age were omitted Amniotic fluid was obtained by abdominal amniocente is When all

Table I Distribution of material

	Patients	Samples
Toxemia		
Mild moderate	1	2
Severe	8	11
Chronic hypertensive vascular disease in pregnancy	9	16
Diabetes mellitus White (A B and C groups)	7	23
Diabetes mellitus White (D E and F groups)	4	12
Rh isoimmunization	29	9
Total	69	176

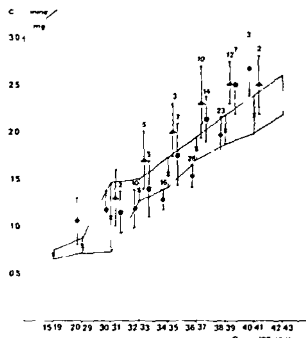


Fig 1 Creatinine concentration (mg %) in amniotic fluid during gestation in complicated pregnancy Each sign represents the means of the number of determinations given in the figure The vertical bars indicate the 95 % confidence interval for each mean The 95 % confidence interval for normal pregnancy is indicated by drawn lines × Normal pregnancy ▲ toxemia ● iso-immunization ■ diabetes

specimens contaminated with blood or meconium had been discarded there remained 176 specimens of amniotic fluid from 69 patients to be examined All specimens were coded and tested blindly The groups studied and the number of patients in each group are shown in Table I

Diagnosis and classification of toxemia of pre- was done according to a recommendation of the Committee on Maternal Welfare issued in 19 diagnosis was based on the presence of at lea following symptoms and signs (A) a re blood pressure of >90 mmHg on several oc (B) persistent moderate to marked oedema (C) proteinuria ≥1+ protein (Albustix) in midstream spe

The patient was specified of having severe one or more of the following criteria were f Resting diastolic blood pressure >100 mmH ment with hydralazine ≥200 mg daily 3) Per proteinuria >3+protein All patients were trea chlorothiazide and all but 6 patients were hydralazine

The White classification was used for the with diabetes mellitus (28)

All mothers with Rhesus isoimmunization had antibodies demonstrated by the indirect Coomb The live born infants were Rhesus positive and tive direct Coombs test

Amniotic fluid samples were obtained in d of pregnancy In most cases 2–4 samples were ta intervals of 1–3 weeks

The values for L/S ratio and creatinine conce normal pregnancy were derived from our pre tion (10)

METHODS

Amniotic fluid was obtained by abdominal am centrifuged for 10 minutes and then fi filter paper (10) Creatinine was analyzed according to Jaffe s method (3) and the other was frozen and stored at −20°C until phospholipid content and L/S ratio (10) In creatinine determination failed for technical rea in 21 cases the determination of L/S-ratio was because of an insufficient amount of liquor

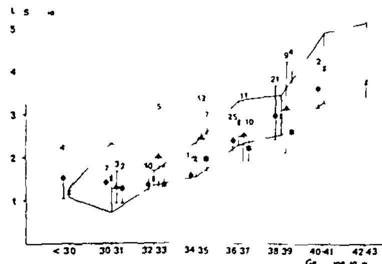


Fig 2 Lecithin Sphingomyelin ratio in amniotic fluid during gestation in complicated pregnancy Each sign represents means of the number of determinations given in the figure The vertical bars indicate the 95 % confidence interval for each mean The 95 % confidence interval for normal pregnancy is indicated by drawn lines × Normal pregnancy ▲ t ● isoimmunization ■ diabetes

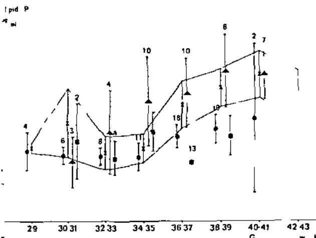


Fig 3 Concentration of phospholipid phosphorus in amniotic fluid during gestation Each sign is mean ±S E of the number of determinations given in the figure The mean ±S E for normal pregnancy is indicated by drawn lines × Normal pregnancy ▲ toxemia ● iso-immunization ■ diabetes

STATISTICAL METHODS

r the assumption that the values in the normal series rmally distributed prediction intervals for each time l were calculated as

D $\sqrt{(n+1)/n}$ $t_{0.975}$ $(n-1)$

t $(n-1)$ is the 97 5th percentile of a t-distribution $n-1$ degrees of freedom The probability that the of a presumptive normal individual falls outside nterval is approximately 5%

each of the pathological groups and for each time l the number of individuals with values outside the sponding normal prediction interval was recorded number follows a binomial distribution with para s n and 0 05 where n is the number of individu the pathological group examined during the specific time interval The probability of obtaining the observed result or a more extreme one was calculated A small probability value indicates that the pathological group has a distribution of values which ought not be regarded as normal

RESULTS

Toxemia This group includes mild and severe toxemia and hypertensive disorders No difference was found between the different subgroups of toxemia and chronic hypertension The mean level of creatinine (Fig 1) was higher in toxemia than in normal pregnancy of the same gestational age The difference was statistically significant ($p<0.05$) from the 32nd week of pregnancy till term The

II *Gestational age (w) and the combination of creatinine (Cr mg %) and L/S ratio in amniotic fluid mal and complicated pregnancies*

mber of samples N=number of patients

	w	S	N	% of S: Cr ≥1 8 and L/S ≥2 25	Either Cr ≥1 8 or L/S ≥2 25: Cr ≥1 8	Either Cr ≥1 8 or L/S ≥2 25: L/S ≥2 25	Cr <1 8 and L/S <2 25
al	≥38	42	42	71	17	10	2
	37–36	5	25	40	1	24	24
	35–30	29	9	0	10	10	80
mmunization	≥38	23	16	57	9	17	17
	37–36	25	23	12	12	40	36
	35–30	31	19	0	0	3	97
	≥38	15	14	87	13	0	0
	37–36	10	10	40	30	10	0
	35–30	19	13	5	59	14	22
	≥38	5	4	60	40	0	0
	37–36	13	10	46	23	23	8
	35–30	14	8	7	21	0	72

Table III *Minimum values of L/S ratio creatinine/AF and gestational age under certain [illegible] and complicated pregnancies*

	Week of pregnancy ≥38		
	Minimum values of L/S ratio	Minimum value of creatinine/AF (mg %)	Minimum [illegible] pregnancy [illegible] Cr ≥1 8 [illegible] L/S ≥2 [illegible]
Normal pregnancy	1 55	1 5	36
Iso Immunization	1 87	1 4	36
Toxemia	1 66	1 9	35
Diabetes	1 80	2 1	35

L/S ratio (Fig 2) was significantly higher in toxemia during the 34th–35th week ($p<0\ 05$) than in normal pregnancy but within the normal range at later times

Rh isoimmunization There was a tendency to lower concentrations of creatinine from the 32nd week of pregnancy until term in this group compared with the normal group (Fig 1) The difference was however not statistically significant The L/S ratios did not deviate significantly from those in normal pregnancy (Fig 2)

Diabetes No difference was found between subgroups of diabetes and they are thus presented as one group The creatinine concentration (Fig 1) in the 36th–37th week was significantly higher ($p<0\ 05$) compared with the normal group The L/S ratio fell within the normal range (Fig 2)

The concentration of total phospholipid in the different groups (Fig 3) showed mainly the same distribution as the normal group

Table II shows the relation between the gestational age and the combination of certain borderline values for L/S ratio and creatinine concentration in different groups of high risk pregnancy In toxemia only 22 % of the samples before the 36th week had a creatinine value <1 8 mg % and a L/S ratio <2 25 The immunization and diabetes groups showed a pattern similar to the normal group

Table III shows the minimum values in pregnancy ≥38th week When the borderline values creatinine concentration ≥1 8 mg % and L/S ratio ≥2 25 were combined the length of gestation never underrated the 35th week neither in the normal nor in the pathological groups of pregnancy

DISCUSSION

In the present report data on a relatively small number of patients are presented Furthermore several amniotic fluid samples have been [illegible] from most of the patients Conclusions [illegible] therefore be drawn with care

In toxemia creatinine concentration [illegible] significantly increased ($p<0\ 05$) from the [illegible] week till term over those in the normal [illegible] 1) This is in accord with recent reports [illegible] 27) but in contrast to others (8 9 11 17 [illegible] reason for the lack of agreement between [illegible] reports is not clear

However differences in classification [illegible] in terms of severity duration of the disease [illegible] of treatment etc may be of importance

The reason for the higher concentration [illegible] creatinine in amniotic fluid in toxemia is not [illegible] It has been suggested that it might be due [illegible] maternal serum creatinine concentration [illegible] decreased rate of transport of creatinine [illegible] amniotic fluid (27) It has also been [illegible] treatment with thiazide diuretics may be [illegible] portance (20) Variation in the amniotic [illegible] ume probably does not affect creatinine [illegible] tion (24) The possibility that maternal [illegible] may pass through the placenta and affect [illegible] function or that placental insufficiency [illegible] creased fetal catabolism has also been [illegible]

In iso immunization the amniotic fluid [illegible] concentration (Fig 1) tended to be low [illegible] was no statistically significant difference [illegible] this group and the normal group It is [illegible] interesting to note that Hinkley et al ([illegible] significantly lower amniotic fluid creatinine [illegible] centration in isoimmunization with [illegible] mg % often accompanying fetal maturity

The amniotic fluid creatinine concentration [illegible] diabetes was within the limits of the [illegible] with the exception of the 36th–37th week [illegible] there was a significant increase ($p<0\ 05$ [illegible]

ıer of patients in this group is small however el that the isolated increase in creatinine con ation should be interpreted with care Slight ase in creatinine concentration in diabetes has reported (25) and was interpreted as a sign of a rapid maturation of the fetus in diabetes ver this conclusion might not be valid for the as a whole as the L/S ratio which is an esti of fetal pulmonary maturity (2 13 14) was n the normal range in diabetes (Fig 2)

L/S ratio deviated significantly from normal ancy only in toxemia and at one time only the 35th week (Fig 2) In iso immunization and tes the L/S ratio was within the normal range ord with Doran et al (9)

early increase in L/S ratio in toxemia com with normal pregnancy is in accord with the g of Gluck et al (12 13 15) They have also ted early increases in L/S ratio in a number of ancies complicated by maternal diseases other oxemia Others however have not found any se in *L/S ratio (6 7 9) or amniotic fluid leci* oncentration (1 2) in any complicated preg In diabetic pregnancies (classes A B and increase L/S ratio was delayed (13) and did cur until 37 weeks of gestation This has been ved by others (23 29) but was not observed r series (Fig 2) As discussed above dis ncies may be due among other things to differ ays of classification of maternal disease In the of the L/S ratio divergent results might also be methodological differences (10)

is been suggested (19) that the synthesis of face active lecithin in the lung (which is the of most of the lecithin in the amniotic fluid) r the influence of the adrenal corticosteroids at this is why an earlier pulmonary maturity be seen in pregnancies with intrauterine fetal s On the other hand in pregnancy with an ephalic fetus where adrenal function should icient both low (1) and normal (4) L/S ratios een reported

high amniotic fluid creatinine concentration emia is of great clinical importance Thus of premature toxemia pregnancies (<36th had creatinine concentrations ≥1 8 mg% is thus a possible risk that the pregnancy be prematurely induced before the fetus has e pulmonary mature if estimation of gesta age is based only on creatinine concentration Table II) To get a more accurate estimate of the gestational age the L/S ratio should also be determined as the use of these two measurements in combination only gives a 5% false positive rate (Table II) The risk of inducing delivery prema turely diminishes considerably in this way

The tendency to low creatinine values in iso immunization (Fig 1) although the values were not significantly lower than normal might still be of clinical importance If the estimation of gestational age is based solely on creatinine concentration some cases might be placed in an incorrectly low group according to Liley This might obviously have severe consequences for the fetus The situa tion can be avoided if the L/S ratio is also de termined Therefore we feel that when gestational age is unknown not only creatinine but also L/S ratio should be determined

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VAGINAL REPAIR IN THE RADICAL OPERATION FOR CERVICAL CARCINOMA

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tract An attempt was made to preserve postoperative ual function and the recovery of bladder function by a ple modification of technique in 22 cases of radical rations for invasive carcinoma of the cervix The pro- ures consisted of two parts After removal of the imen the bladder peritoneal flap is sutured to the nor vaginal wall leaving a 2 to 3 cm margin between line of suture and the edge of the peritoneum Similar the posterior peritoneal flap is sutured to posterior inal wall leaving a margin Both edges of the toneum are then closed forming a pouch as an exten i of vaginal canal The length of the vagina was suc fully elongated by this procedure thus adding to bet postoperative sexual function

dical hysterectomy with pelvic lymph nectomy has been commonly performed for the itment of first and second stage carcinoma of the vix in Japan The surgical procedures were ed principally on the Okabayashi method and rative techniques were further developed by no Hashimoto Magara Kobayashi et al The or problems of radical hysterectomy are the nary mortality urinary tract complications such infection fistula formation ureteric stricture dder atony and shortening of the vagina (2 3)

he primary mortality rate however has di ished significantly and the incidence of erovaginal vesicovaginal and rectovaginal ilae also markedly decreased by the improve it of operative techniques (4 5) Remaining olems are the prevention of bladder atony eric stricture and shortening of the vagina toperative sex life is frequently disturbed as a ilt of a short vagina The present study was ied out with the intent of preserving the sex life r the operation by modifying vaginal repair iniques and accelerating the recovery of the bladder function by fixing the bladder to the vaginal wall

MATERIALS AND METHODS

The total number of patients subjected to this modified techniques was 2? including 9 patients with stage I B 1 stage II A ? stage II-B 9 stage III B and I stage IV These patients were managed surgically after the Okabayashi method at the Tokyo Medical and Dental University Hospital during 1971–1972

The characteristics of the Okabayashi method are as follows 1) At first the pelvic lymph nodes are removed by block dissection along the external iliac vein obturator nerve internal iliac vein and the cardinal ligament and down the side of the pelvic wall 2) The uterine ligaments e g cardinal rectovaginal and vesicovaginal ligaments are isolated and dissected separately 3) The ureter should be stripped off preserving the adventitia and fine paraureteric tissues especially in the region between its crossing with the uterine artery and the bladder 4) The vagina can be sufficiently detached and dissected a re quired including the areas of cancer infiltration so that the line of dissection is at least 2 to 3 cm clear of carcinomat ous involvement

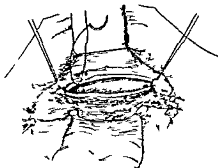


Fig 1 Ligatures of No I chromic catgut are placed on the anterior vaginal wall for hemostatis

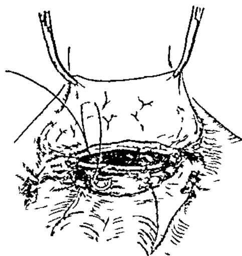


Fig 2 The bladder flap is attached to the anterior vaginal wall using the same suture of chromic catgut

In this study certain procedures are added to the original radical operation as follows 1) The bladder peritoneum is detached at the uterine reflexion so that a sufficiently wide peritoneal cuff is left Similarly the posterior peritoneum is dissected 2) Vaginal repair is completed after the specimen has been removed Three to four ligatures of No 1 chromic catgut are placed on the anterior vaginal wall not including the vaginal epithelium for hemostatis (Fig 1) 3) Then the same interrupted sutures are used to attach the bladder peritoneal flap to the anterior vaginal wall the bites being taken ? to 3 cm from the edge of the peritoneal cuff When all the sutures are placed a margin of 2 to 3 cm of peritoneum is left free from sutures (Figs 2 and 3) 4) In the same manner sutures are placed on the posterior peritoneum and the posterior vaginal wall (Fig 4) 5) The edges of the anterior and posterior peritoneum are sutured together with interrupted 00 plain catgut to form a peritoneal pouch as an extention of the vaginal canal (Figs 5 and 6) Two drains are inserted through the abdominal wall into the dead space on both sides deep in the pelvis

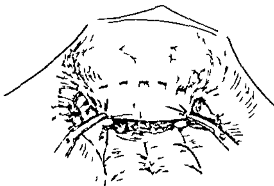


Fig 3 A margin of bladder peritoneal flap of 2 to 3 cm width is left free from sutures

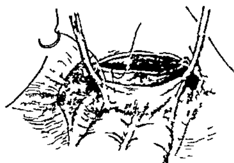


Fig 4 Sutures are placed on the posterior vag[illegible] and the posterior peritoneum in the same ma[illegible]

An indwelling catheter was used for 7 da[illegible] operation The volume of residual urine after each [illegible] was measured thereafter By the 10th to 14th p[illegible] tive day the peritoneum forming the vaginal pouc[illegible] grey and adhesions form readily Serous and [illegible] charge is observed Digital separation and [illegible] application of antibiotics may be useful The per[illegible] gradually undergoes necrosis but in about [illegible] peritoneal pouch is completely replaced by new [illegible] epithelium The duration of admission is usua[illegible] but 2 months or more are required when ext[illegible] tion is performed

Seventeen of 2? patients received postoperati[illegible] nal irradiation to the pelvis These 17 patien[illegible] metastases in the pelvic lymphnodes parametr[illegible] or extensive infiltration of the cervix

Patients were followed every 3 months by pel[illegible] rectal examinations Renal function studies [illegible] intravenous pyelography and other labora[illegible] done as required Patients were advised to re[illegible] intercourse soon after leaving the hospital The l[illegible] the vagina was measured about 1? to 1 yea[illegible] operation and the woman's sex life was [illegible] personally in detail These results were com[illegible]

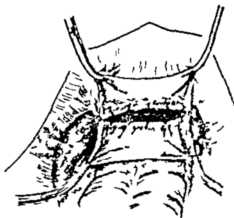
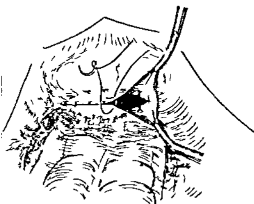


Fig 5 A margin of rectal peritoneal fla[illegible] sutures



6 The edges of the anterior and the posterior toneum are sutured together to form a peritoneal h as an extention of vaginal canal

of 36 subjects with radical operation for invasive ical carcinoma performed during 1968 to 1970 with his modification

RESULTS

measurement of the length was made along the rior wall of the vagina The mean of the length he vagina in 22 patients was 6 6 cm ranging from to 7 5 cm in contrast to 4 9 cm in 36 control jects without this procedure In the study group vagina could be further lengthened another 1 to n by the application of pressure at the vault

pontaneous urination usually starts on the day n the indwelling catheter is removed The mean 8 5 days after the operation whereas in the trol group it was 12 6 days It took 25 3 days on rage before the residual urine was constantly than 50 ml in the study group The range was n 14 to 62 days In the control group it was 27 6 s

f the 22 patients 8 (36%) reported their sex life atisfactory and 9 (40%) noted some discomfort no patients had serious complaints In the con group 65% had a mild to severe sexual dis bance and 20% had no complaint in this regard

reterovaginal fistula was found in 1 out of 22 ly cases and 1 in the control group There was incidence of vesicovaginal and rectovaginal ila One recurrence of carcinoma in the vaginal np was found in the control group Two of the ases died with recurrence at the pelvic wall and astases in the ascending lymphnodes respec ly within 2 years of the operation

DISCUSSION

The first principle to be observed in the surgical treatment of cervical carcinoma is a radical opera tion but its magnitude may lead to the occurrence of serious postoperative complications Careful and complete removal of the pelvic lymphnodes is ex pected to raise the 5 year survival rate The inci dence of recurrence is higher in the presence of pelvic lymphnode metastases Wide dissection of the vaginal wall and complete isolation of the blad der and ureter often results in fistula formation *urinary bladder dysfunction and shortening of the* vagina Wrapping the ureter with pelvic peritoneum or intraperitoneal replacement of the ureter has been employed to prevent ureteric fistula and post operative hydronephrosis These procedures can prevent displacement of the ureter toward the pelvic wall by scar formation and kinking and can also avoid its malnutrition when placed ex traperitoneally

The use of bougies dilatation of the urethra diathermy incision of the sphincter muscle at the urethro-vesical junction are reported to be helpful in relieving urinary symptoms caused by bladder atony In this study the modification was made so that postoperative sexual disturbance due to shortened vagina and bladder dysfunction may be lessened Improvement was found in vaginal length vaginal flexibility and postoperative sexual func tion but the fixation of the bladder to the vagina did not improve bladder function The use of peritoneum in the construction of a vagina was de scribed by other authors (6) We also have one case of aplasia of the vagina treated by the same princi ple with a good result The isolation and preserva tion of pelvic parasympathetic nerves from the car dinal ligament and paracervical tissue (7) and pre servation of the vesical artery (8) were reported to facilitate recovery of bladder function especially in the early stages of cervical carcinoma Adoption of these techniques is to be considered to obtain further improvement of bladder function

Incidence of ureterovaginal fistula 1 out of 22 cases or 2 out of total 58 cases is not particularly low compared to other studies Extensive invasion *of the paracervical tissue and resulting difficulty in* preserving paraureteric tissue may be the reason for the fistula formation

Recurrence at the vaginal stump was found only in 1 out of 58 cases This low incidence of local recurrence may be one of the characteristics of the

Okabayashi operation However a short vagina of about 4 to 5 cm in length is formed as a result if no modification of the original procedure is made Generally without modification the vagina becomes fibrous and rigid after operation Although lack of sex desire or avoidance of sexual activity after the operation was found in 5 of 22 cases (22%) improved sexual function realized by the new technique indicates that the major factor causing the sexual disturbance is the shortened vagina and lack of distension of the vaginal pouch

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THE EFFECT OF A COPPER IUD AND VARIOUS INERT' IUDS ON THE HISTOLOGICAL PICTURE OF THE RABBIT ENDOMETRIUM DURING EARLY PSEUDOPREGNANCY AND PREGNANCY

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act The influence of a copper IUD and two inert on the histological picture of the rabbit en trium during early pseudopregnancy and early preg y was studied The copper IUD markedly inhibited ndometrial maturation during the first five days of pseudopregnancy and pregnancy The inert IUDs o such effect The copper IUD prevented the normal nse of the rabbit uterus to 17 beta estradiol in ated animals The observed effects of the copper might seriously interfere with the normal process of ntation

ral authors report that inert IUDs in wom ave traumatic effects on the endometrium local pressure atrophy superficial endometrial on endometrial necrosis stromal oedema osity and dilatation of capillaries and iorrhages (6 7 19 20 22 24 32 35 37 47) aumatic effects are also described in various imental animals (2 8 9 27 28 30) Most of effects are localized in the proximity of the An *increase* in inflammatory cells in the metrium and in the uterine lumen is usually ot always found in women (4 6 17 18 22 24 I 37 35 38 39 40 48) and in experimental ils (10 14 21 33 36 43) fitted with inert opper IUDs This inflammatory reaction was l in the absence of infection (31) In rats and eys a copper IUD caused a more marked imatory response than did a plastic IUD (10) relation between the number of inflammatory and the reduction of fertility has been ved (33 36)

effect of IUDs on the normal maturation of ndometrium has been studied in several species Most of the reports on women wearing IUDs found no change in the normal development of the endometrium (17 20 24 40) Evidence supporting a premature development was presented by Wynn (44 45 46) whereas others (4 6 37 47) reported a delayed development In rats the de cidual reaction is inhibited by inert IUDs (9 12 23 26 29) and by a copper IUD (41) Zipper in his original work (47) on the effect of a copper IUD on the rabbit endometrium reported an intense prolif eration of the mucosal stroma However Abraham (1) found no morphological changes in the presence of a copper IUD during the first four days of pregnancy in the rabbit

In two previous reports (15 16) a copper IUD was found to inhibit the DNA synthesis in the endometrium during early pseudopregnancy and pregnancy in the rabbit This suggests an improper maturation of the endometrium The present study therefore investigated the effect of a copper IUD and various inert IUDs on the morphology of the rabbit endometrium during the first five days of pseudopregnancy and pregnancy

MATERIAL AND METHODS

Virgin rabbits of mixed breed weighing two to three kg were used Three types of IUDs were studied 1) Copper IUD—consisting of a 50 mm long polyethylene catheter 0 5 mm in outer diameter (Clay Adams Parsippany N Y USA) around which a copper wire 0 23 mm in diameter was coiled giving a surface area of 00 mm² (*Cu IUD*) 2) Platinum IUD—identical with the Cu IUD except for the change of metals (Pt IUD) 3) Plastic IUD—consisting of a polyethylene catheter 1 0 mm in outer diameter and 50 mm long (*Pl IUD*)

Table I *Presentation of various experimental groups with number of animals and main effects of types of IUDs*

Group	Combinations of IUDs	Subgroups (hours)	No of animals	Main histological effects of IUDs
I	Pl IUD$_{1\cdot 0}$ SH (stimulated with HCG)	0 48 120	5 4 3	In horns fitted with the *Pl IUD$_{1\cdot 0}$* as compared with operated horns (in all subgroups) erosion of e mucosal necroses increased number of inflamm
II	Pl IUD$_{1\cdot 0}$ Pt IUD (stimulated with HCG)	0 48 120	4 4 4	In horns carrying the *Pt IUD* as compared with containing horns increased number of eosinophil were seen Otherwise the same changes as noted Pl IUD$_{1\cdot 0}$ but with more frequent mucosal necrose
III	Pl IUD$_{1\cdot 0}$ Cu IUD (stimulated with HCG)	0 48 72 120	3 5 5 5	In horns fitted with the *Cu IUD* as compared with containing horns at *0 hours* swollen epithelial c glands At *48–72 hours* less pronounced prea tion of the surface epithelium less minor fo glands few mitotic figures At *120 hours* reduced of minor folds with fewer interconnecting bridg glands In all subgroups increased inflammatory and more frequent necroses
IV	Pl IUD$_{1\cdot 0}$ Cu IUD (mated animals)	0 60 120	7 6 6	In horns fitted with the *Cu IUD* the same cha scribed in Group III
V	Pl IUD$_{1\cdot 0}$ Cu IUD (castrated estrogen treated animals)	0	3	In horns fitted with the *Cu IUD* a poor respons gen with low cuboidal flattened epithelium li glands mucosal necroses a marked inflammatory and a reduced diameter of the uterine horn

The IUDs were sterilized by soaking in ethanol and rinsed in sterile physiological saline before use The animals were anaesthetized with Nembutal and the abdominal cavity was exposed under sterile conditions via a lower midline incision No corpora lutea were present at the operation The IUDs were introduced into the uterine just above the utero-cervical junction the lower d of the IUDs being fixed to the uterine wall by a 4 0 silk suture at the puncture Uterine horns designated sham operated (SH) were exposed to introduction and withdrawal of the Pl IUD$_{1\cdot 0}$ a 4-0 silk suture being placed in the antimesometrial wall

The effect of the different IUDs was compared with the effect of the Pl IUD$_{1\cdot 0}$ Thus one horn was always fitted with a Pl IUD and the other with one of the other types of IUDs in all groups except in the group where one horn was sham-operated The IUDs were always randomized between the horns The rabbits were divided into five groups according to the combinations of IUDs (Table I)

On the fifth day after operation most of the animals were given 75 IU of HCG (HCG human chorionic gonadotropin Gonadex Leo AB Helsingborg Sweden) intravenously to induce pseudopregnancy or mated with fertile bucks The animals were subsequently killed by cervical dislocation at various times up to 120 hours after injection or mating Some animals—killed on the fifth day after operation corresponding to 0 hours—received no HCG injection The mated animals were killed immediately after mating In one group (Table I Group V) three animals castrated for at least two months and fitted with the Pl IUD$_{1\cdot 0}$ and the Cu IUD were injected with 1 µg 17 beta oestradiol per kg bodyweight for 1 beginning 48 hours after the insertion of the IUT

The internal genitalia were taken out and the horns were trimmed The presence of corpora each ovary was registered The uterine horn responded to the length of the IUD was c IUD part A part of the midportion of the IUD fixed in Bouins solution All specimens were em paraffin and the sections were stained with he and eosin

RESULTS

In one group of animals one horn was operated and the other was fitted with the Pl (Table I Group I) In sham-operated horns *at 0 hours* (unstimulated animals Fig 1 major mucosal folds were lined by a s columnar epithelium as were the few gl glands Very few mitotic figures were pres endometrial stroma had the appeara connective tissue rich in small capillary ves prominent endothelial cells Few neutroph cytes were seen

At 48 hours (Fig 1 B) the surface epithel pseudostratified and the numerous and l were also partly lined by a pseudostr



Maturation of the endometrium in sham-operated (Fig 1 A B and C at 0 48 and 120 hours after stimulation respectively) in horns fitted with the D a (Fig 1 D E and F at 0 60 and 120 hours p c tively) and in horns fitted with the Cup-IUD (Fig 1 and I at 0 60 and 120 hours p c respectively) are no apparent differences between sham-operated and Pl IUD containing horns (cf Fig 1 A C to Fig 1 D–F) In the presence of the Cu IUD there is an inhibition of the maturation of the endometrium as compared with Pl IUD, horns (cf Fig 1 G–I to Fig 1 D–F) the comparison is made between horns within the same animal (×? 64)

m Minor folds appeared and in some areas s between them were formed Mitoses were lant both in the surface and in the glandular lium In the minor mucosal folds the stroma ired as thin septa Numerous sinusoidal ves vere seen beneath the epithelium Occasion ocal interstitial oedema was seen in the stroma rell as swollen fibroblasts Only very few ~ytes were present

120 hours (Fig 1 C) the minor mucosal folds now very pronounced as were the bridges en adjacent folds The surface epithelium was pseudostratified whereas the glands were mainly lined by a single layered columnar epithelium Single mitotic figures were seen Only a few specimens showed a columnar epithelium with protruding cytoplasm at the top of mucosal folds A very thin stromal lining containing sinusoidal vessels was found between the epithelium of the mucosal folds and between the glands No leucocytes were found

In the contralateral horn of these rabbits fitted with the Pl IUD₁₀ the above described histological picture was generally repeated (Fig 1 D E and F Fig 2 A B and C) However at all times after HCG stimulation areas of local erosion sometimes



Fig 2 Pictures of Pl IUD ,(Fig 2 A B and C at 0 60 and 170 hours p c respectively) and Cu IUD-containing horns (Fig 2 D E and F at 0 60 and 170 hours p c respectively) The comparison is made between horns within the same animal In the presence of the IUD there is a reduced number of glands (cf Fig 2 D) and a less pronounced minor [illegible] and C to Fig 2 E and F) (×30)

ing to mucosal necrosis were seen The r of inflammatory cells was greater in the etrium and in the uterine lumen

histological picture of the endometrium de l above for horns fitted with the Pl IUD_{10} ways found in horns fitted with this IUD ctive of the treatment of the contralateral Sham-operation Pt IUD Cu IUD Groups able I)

e presence of the Pt IUD (Table I Group II) tological picture was almost identical with the Pl IUD_{10}-containing horns However in nimals the Pt IUD caused a more prominent al inflammation and there was an abundance nophil leucocytes mainly localized just be he epithelium

same histological changes were observed in esence of the copper IUD both in HCG ted (Table I Group III) and mated animals I Group IV)

hours the Cu IUD caused more prominent is and mucosal necrosis than did the Pl $_{10}$ The appearance of the epithelium was in the presence of both types of IUDs but i areas in the presence of the Cu IUD d a thicker epithelium sometimes with a anized orientation of the cells Swollen cells also found in these and in other areas of the lium The number of glands was reduced in esence of the Cu IUD The glands were lined single layered columnar epithelium in the ce of both types of IUDs (Fig 1 D and G A and D) The Cu IUD evoked a more unced inflammatory response and there was undance of both neutrophil and eosinophil ytes in the endometrium and in the uterine

8 to 72 hours the proliferation was markedly ed in the copper influenced endometrium as number of glands were reduced the ostratification of the epithelium was less pro ed the minor folds were fewer and smaller he number of mitotic figures seemed to be ed (Fig 1 E and H Fig 2 B and E) In certain of the surface epithelium some swollen cells seen The inflammatory response was in ed in the Cu IUD-containing horn Also at times there was an abundance of leucocytes vacuoles often containing inflammatory were frequently seen in the copper influenced ce epithelium

At 120 hours the inhibition of the endometrial maturation in the presence of the Cu IUD was even more evident as seen in a smaller number of endometrial glands and especially in a marked reduction of the development of minor mucosal folds with fewer interconnecting bridges (Fig 1 F and I Fig 2 C and F) In addition the inflamma tory response was higher in the copper influenced horns with a large number of leucocytes Mucosal erosions and necroses were noted In the copper influenced horns the sinusoidal character of the vessels was less evident than in the Pl IUD_{10} influenced horns

In one group castrated and estrogen treated ani mals fitted with the Pl IUD_{10} and the Cu IUD were studied Horns containing the Pl IUD_{10} had almost the same appearance as that found in estrus rabbits (Fig 3 A) The major folds were lined with a high columnar epithelium as were the normal appearing glands (Fig 3 B) In the copper influenced horns the small major folds were lined with a low cuboidal epithelium and very few glands were seen (Fig 3 C and D) Furthermore the diameter of these horns was markedly reduced (cf Fig 3 A and C) A marked inflammatory response and areas of mucosal necrosis were also seen

DISCUSSION

The appearance of the histological picture of the endometrium in the sham-operated horns (of ani mals fitted with the Pl IUD_{10} in the control horn) agreed well with earlier reports on the maturation of the endometrium during early pseudopregnancy of the rabbit (11) The present study revealed no obvious differences between the appearance of the endometrium in pregnancy and in pseudopregnan cy This is somewhat at variance with the results of Beier & Kuhnel (5) who stated that the uterine epithelium underwent symplastic transformation between the 4th and 5th day in pseudopregnancy and between the 5th and 6th day in normal preg nancy This discrepancy might be due to different strains of animals and also to the dose of HCG used (in our study 75 IU Beier & Kuhnel s study 50 IU)

As the mere presence of an inert IUD might cause changes of the histological picture of the endometrium the effects of the Pt IUD and the Cu IUD were compared with the effect of the Pl IUD_{10} which was always inserted into the con tralateral horn

All types of IUDs studied in the present investi



Fig 3 Appearance of Pl IUD_{10} (Fig 3 A and B) and Cu IUD-containing horns (Fig 3 C and D) in castrated and estrogen treated animals The comparison is made between horns within the same animal There is [...] response to estrogen in the Cu IUD-influenced [...] Fig 3 A and C ×30 Fig 3 B and D)

gation caused endometrial erosions and mucosal necrosis These traumatic effects were more pronounced in the presence of the Pt IUD and the Cu IUD than in the presence of the Pl IUD_{10} Earlier several authors (2 8 28) described such effects of IUDs in rabbits

The presence of a copper IUD also caused a more marked inflammatory response in our rabbits than did the inert IUDs This finding agrees well with the report by Cuadros & Hirsch (10) However Hagenfeldt (17) described only a mild inflammatory response in human wearers of the Cu T 200 and Salaverry et al (38) found no inflammatory reaction at all

Abraham (1) found no effect of a copper IUD on the histological picture of the rabbit endometrium during the first four days of pregnancy [...] Zipper et al (47) found an intense prolifera[...] the rabbit mucosal stroma in the prese[...] copper IUD Zipper et al interpreted the[...] as an increased sensitivity of the e[...] estrogen Aedo & Zipper (3) also [...] increased uptake of estrogen in the prese[...] copper IUD in the rat In contrast we f[...] response to estrogen in castrated es[...] rabbits in the presence of the copper IU[...] development of the endometrium was [...] inhibited furthermore the epithelial ce[...] uterine cavity were cuboidal and not of [...] columnar type as would be expe[...] estrogen influenced endometrium (13) I[...] the reduced number of glands in t[...]

nced horns of oestrus rabbits at 0 hours might a decreased responsiveness of the en trium to endogenous estrogen

m the present study it is obvious that the JD in contrast to inert IUDs caused a ed inhibition of the proliferation and develop of the endometrium As far as we know this of the copper IUD has not previously been ibed In two earlier studies (15 16) the DNA esis of the endometrium was reported to be icantly inhibited by the presence of the Cu which is in good agreement with the inhibition proliferation described in this paper

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PLASMA AND URINARY OESTRIOL DURING LATE UNCOMPLICATED PREGNANCY

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act Plasma levels of unconjugated oestriol and uri excretion of conjugated oestriol were measured in ealthy women with uncomplicated late pregnancy vith normal renal function Considerably larger dif es within or between days were noted for the a levels than for the urinary excretion of oestriol ·icant correlation between plasma levels and urinary tion was found in only three out of ten patients Due ? large variations within and between days the esti n of unconjugated oestriol in plasma might be un ;le as a substitute for the estimation of urinary conju oestriol in the supervision of complicated preg ·s

iation of the urinary excretion of oestriol or oestrogens has been used for the supervision ,h risk pregnancies for nearly 20 years (for a w see Frandsen 1963) Due to the variability excretion it is desirable to perform serial s using minimum 24 hour samples (7) How a complete 24-hour urine collection is difficult omplish even in lying in patients Moreover elay implicit in the collection of a 24-hour nen might cause loss of valuable time It is ise of these disadvantages that many in gators have advocated plasma analyses for the oring of high risk pregnancies 90% of the ol in peripheral plasma is conjugated mainly icuronic and sulphuric acids Estimation of gated oestriol in plasma will therefore nor include hydrolysis of the conjugates before sis This step is not included in the assay of ijugated oestriol and this assay will therefore ore rapid The purpose of the present inves on was to study the inter relationship between asma levels of unconjugated oestriol and the y oestriol excretion during the last month of nplicated pregnancy

MATERIALS AND METHODS

Patients

Ten healthy women with uncomplicated pregnancies were studied All subsequently gave birth to single infants with birth weight exceeding 2 500 g .4-hour urinary specimens were collected twice a week from the 36th week of preg nancy During each sampling day blood samples were drawn into heparinized Vacutainers® at 08 00 a m 08 00 p m and 08 00 a m After centrifugation the plasma was stored at −20°C until analysis

Methods

The plasma levels of unconjugated oestriol were estimated by radioimmunoassay as described by Lindberg et al (8) Urinary oestriol concentrations were estimated according to Frandsen (6) All oestriol assays were performed in duplicates In order to investigate the renal function and to correct for the possibility of incomplete urine collection creatinine in plasma and urine was analysed using the Technicon method at the Department of Clinical Chemistry University Hospital Uppsala The osmolality of the urine was estimated by measuring the depression of the freezing point

Statistical methods

To investigate the possibilities to predict urinary excretion of oestriol from plasma levels the coefficients of correla tion were calculated between urinary excretion and each of the three blood samples The following notations were used n = number of sampling days x = oestriol (ng/ml) in plasma at 08 00 a m the first morning of the sampling day x_2 = oestriol (ng/ml) in plasma at 08 00 p m x_3 = oestriol (ng/ml) in plasma at 08 00 a m the following day y = uri nary oestriol in mg/24 hour or urinary oestriol in µg/mg of creatinine S = S D of y r = coefficient of correlation between y and x

In Table I the coefficients of correlation significant ly different from zero are denoted by $=P \leq 0.05$ $=P \leq 0.01$ and $P \leq 0.001$

RESULTS

The analysis of plasma and urinary creatinine re vealed a normal renal function in all patients The

Table I *The correlation between plasma levels of oestriol (x) and the urinary excretion calculated per 24 hours and per mg creatinine respectively*

The abbreviations are explained in the chapter statistical methods to which the reader should ref the table On some occasions the creatinine values in urine were not measured which explains the d of sampling days (=n) used for the statistical analysis in the two columns

	y = oestriol/24 h									y = μg oestric	
Patient	n	x_1	x_2	x_3	y	S_y	r_1	r_2	r_3	n	x_1
B	6	17 8	15 3	18 7	34 8	4 6	−0 26	0 59	0 37	6	17 8
A	8	14 8	13 4	12 7	24 5	4 8	0 55	0 67	0 47	8	14 8
D	10	21 1	21 6	20 3	23 4	5 0	0 41	0 35	−0 34	9	20 7
G	10	13 8	16 1	11 3	27 0	4 7	0 17	−0 17	−0 13	9	13 5
K	10	16 4	15 4	16 6	44 0	8 9	0 18	0 30	0 30	9	15 6
L	12	7 7	8 8	8 9	18 4	4 8	0 57	0 77	−0 78	10	6 9
M	13	11 3	12 1	12 0	28 4	4 6	−0 70	0 67	0 61	11	11 3
N	5	10 0	12 0	10 2	15 5	1 5	−0 43	0 68	0 50	5	10 0
S	8	12 3	16 5	12 3	21 9	3 5	0 48	−0 31	0 61	8	1 3
W	11	22 5	20 8	19 5	39 2	13 4	0 69	0 55	0 15	9	21 7

plasma levels of unconjugated oestriol showed considerable variations Differences amounting to 15 ng/ml within one 24-hour period were noted on one occasion in three patients The remaining patients displayed considerably less variation within as well as between days

The values for the urinary oestriol excretion varied less than the plasma levels On one occasion one patient had a difference between two days of more than 15 mg/24 hours but in most cases the differences were less than 5 mg/24 hours

The correlation between the total amount of oestriol per 24 hour urinary specimen and the amount of oestriol per mg of creatinine was highly significant indicating an almost complete urine collection The correlation between plasma oestriol levels and the 24-hour excretion of oestriol was significant only in three out of ten patients (Table I) Two of these patients had a significant correlation between plasma concentrations of oestriol and urinary oestriol per mg of creatinine while no such correlation could be demonstrated for the third patient It should be noted that the coefficients of correlation have a large variation and even negative values occur There seems to be no effect of the time of blood sampling during the day upon the correlation between the plasma and urinary values

DISCUSSION

The concentration of unconjugated oestriol in plasma is dependent upon several factors The rate of production in the feto-placental unit tion of the steroid in the body flu transformations during the enterohep tion and the conjugation capacity in liver (For reviews of this subject see Levitz 1970 and Diczfalusy 1974) excretion of oestriol is in addition dep the renal function as a diminished r will give a reduced renal clearance for sulting in high plasma levels and a lo cretion (1) However the renal fun tio in all patients included in the present s

The findings of large variations w tween days for the plasma levels of u oestriol is in accordance with previou another group of healthy women (9) I fluctuations do not reach the fetal below 4 ng/ml reported for patie eclampsia (10) and thus might be i portance

The lack of significant correla plasma concentrations of unconjuga the urinary excretion of oestriol m patients in the present investigation several factors To a certain extent determination may contribute to this lation The coefficient of variation f oestriol method in these ranges was 1 urinary oestriol method 11% M re fact that the non conjugated oestr only 10% of the total oestriol in plas a constant production rate in the fe p

S	r_1	r_2	r_3
3 7	−0 09	0 64	0 33
2 4	−0 03	0 60	0 39
3 8	0 48	0 36	−0 3?
3 ?	0 30	−0 43	−0 24
5 6	0 56	−0 58	0 40
3 7	0 75	0 88 *	0 58
1 9	−0 15	0 54	−0 10
2.7	0 70	0 79	0 43
3 0	0 68	−0 32	0 60
6 7	0 87	−0 55	−0 30

marginal changes in the rates of formation or olysis of the conjugates might cause large al ions in the unconjugated oestriol levels

ontrary to the estimation of unconjugated iol in plasma measurements of conjugated or plasma oestriol yield results with good correla to the urinary excretion values (4 5) Estima of conjugated plasma oestriol has hitherto been time consuming due to the hydrolytic step ved However direct radio immunoassays on ated plasma using suitable antibodies against estriol conjugates in combination with ^{125}I or labelled tracers might certainly appear in the e Such a method will offer a very rapid tech for the plasma determinations and might aps substitute the urinary oestriol assay as the reliable parameter for the monitoring of fetal being At present however urinary oestriol de ination will still be the method of choice for this ose provided that proper and specific methods are used In many routine urinary oestriol methods the specificity has been deplorably neglected in order to gain marginal savings of labour

ACKNOWLEDGEMENTS

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ANNOUNCEMENTS

VIII Akademische Tagung deutschsprechender Hochschullehrer in der Gynakologie und Geburtshilfe Wien 13–18 Juni 1977 Anfragen sind zu richten an Prof Dr H Husslein c/o Wiener Medizinische Akademie Alser Straße 4 A 1090 Wien Austria Tel (0222) 427165 Telegramme Medacad Wien

An International Conference on The Human Vagina Biological and Clinical Aspects will be held at Wayne State University School of Medicine Detroit on October 28–30 1976 (following FIGO meeting in Mexico City) Forty five national and international experts have been invited to discuss the embryology morphology anatomy ultrastructure cytology physiology [illegible] pharmacology immunology microbiology [illegible] the vagina with special emphasis on [illegible] intersexuality congenital defects secretion [illegible]tricial & non-obstetricial injuries bacterial & [illegible]tions plastic surgery and vaginal contra[illegible] accreditation Deadline to submit abstracts of [illegible] research papers July 1 1976 For [illegible] additional information Dr E S E Hafez [illegible] Physiology Laboratories C S Mott Center [illegible] Growth and Development Wayne State [illegible] School of Medicine Detroit Michigan [illegible] 577 1011)

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A NEW TECHNIQUE FOR MEASUREMENTS OF THE URETHRA PRESSURE PROFILE

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ract A new standardized technique for continuous rding of the urethral pressure profile simultaneously intravesical pressure has been developed The pres s were recorded using two micro-transducers en d in a thin Dacron catheter The catheter moved with nstant speed through the urethra with the aid of a ially designed instrument This instrument is de ed Twenty five healthy women were examined The nts were divided into two groups (A) 10 post opausal women and (B) 15 fertile women The results e recordings showed that the functional length and the lute length of the urethra could be reproduced with an r of <1 mm The maximal pressure amplitude was ficantly less in group A

DEFINITIONS

hral pressure=The pressure within the urethra corded in relation to the atmospheric pressure

vesical pressure=The pressure within the adder recorded in relation to the atmospheric essure

hral pressure profile=Recording of the in aluminal pressure at every point throughout the tire length of the urethra (4)

hral closure pressure=The intraurethral pres re minus the bladder pressure (5)

he authors definitions

absolute length of the urethra=The distance tween that point of the urethra where the in aurethral pressure exceeds the bladder pressure d that point where the intraurethral pressure lls to atmospheric pressure

functional length of the urethra=The part of e urethra where the intraluminal pressure ex eds the bladder pressure

ll pressures in mmHg Lengths in mm

INTRODUCTION

The urethra is a tubular structure only about 3 cm long in women It can be described as a biological valve which keeps the urinary reservoir closed If the pressure in the urethra at only one point under all conditions exceeds the bladder pressure the urine cannot escape the urethra (5) In healthy women the urine is allowed to pass merely for short periods during micturition The lumen of the urethra then seldom exceeds 4 mm (9) The sum of the forces which keep the urethral mucous membrane in position varies from point to point throughout its length These forces are a combina tion of active and passive components both in the urethra itself and in the surrounding tissues (7)

In recent years there has been an increased in terest in recording the continuous urethral pressure profile (4 6) If reliable measurements of the urethral pressure profile could be performed espe cially in relation to the intravesical pressure very important information about urethral function could be obtained such as (1) the absolute length of the urethra (2) the functional length of the urethra and (3) the localization of that part of the urethra where the maximal intraluminal pressure is present at rest

Previous techniques for measurements of the urethral intraluminal pressure and the urethral pres sure profile have mainly been based on the use of open end fluidfilled catheter systems or fluid filled balloon catheter systems In both cases the cathe ters are connected to conventional transducers The disadvantages of such catheter systems in measurements of the urethral pressure profile have been analyzed previously (1 3)

We have previously described and tested a new technique for simultaneous intravesical and in

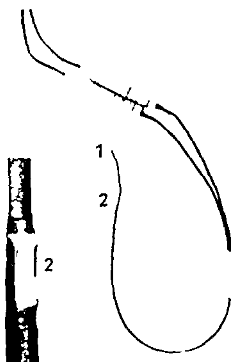


Fig 1 Catheter used for recording of the intravesical and intraurethral pressure The pressure is recorded from the two micro-transducers nos 1 and 2 enclosed in the catheter 6 cm apart Transducer no 2 is demonstrated enlarged six times

traurethral pressure recording (1 3) The result of this test showed that the new technique should be excellent for continuous urethral pressure profile measurements on the condition that the catheter could be moved at a constant speed through the urethra (6) For this reason a special instrument had to be developed

The present investigation was undertaken in order to verify this statement

THE PRESENT TECHNIQUE

A new technique for simultaneous measurements of the intravesical and intraurethral pressure has been presented previously (1 3) In a Dacron catheter 36 cm long with an outer diameter of 5-7 F two micro-transducers (Millar Instruments Inc Houston Texas USA) were mounted 6 cm apart (Fig 1) These micro-transducers have a frequency response of more than 2000 Hz and no zero or temperature drift The catheter was connected to an amplifier Not only the signals from the two ... were amplified but also the difference between signals A Mingograph (EMT 81 Siemens Stockholm Sweden) was used as a recorder ... ment (Fig 2 left) was designed in order to ... sible to record continuously the intraluminal ... every point throughout the length of the urethral pressure profile) This instrument ... following parts *A mobile stand* with a ... device *A motor* attached to the stand A ... mounted to the motor which can be brought ... backwards at a constant speed with the aid of ... As can be seen in Fig 2 (right) there is a ... outer part of the steering arm on which ... easily can be mounted The motor and th... can be set in different angles as seen in Fig ... quently the catheter can be placed so ... of withdrawal follows the anatomy ... end of the withdrawal motor there is a sw... positions one for insertion one for ... for withdrawal When the electric current is ... the steering arm moves with a ... sec With the aid of the switch the withd... halted at any time This makes it poss... intraluminal pressure at any point in the ...

Calibration and sterilisation

Static and dynamic calibration as well as ... place in the calibrator unit previously de... Asmussen Lindström & Ulmsten ( ) The ... calibrator consisted of urolocid solution (... ammonium chloride) facilitating simulta... and disinfection of the catheter

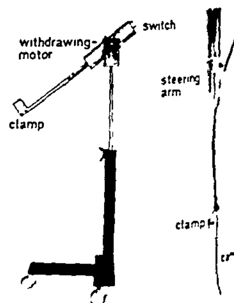
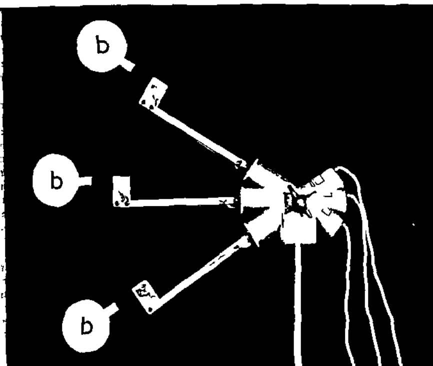


Fig 2 The withdrawal apparatus To the left ... stand with the withdrawal motor attached To the ... the catheter mounted on the steering arm ... the clamp

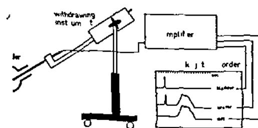
1 F (French) = 0 33 mm



-3 The figure shows that the motor and steering arm be placed at different angles in order to follow the ection of the urethra.

mination of the patients

patient was placed in the lithotomy position The der was filled with 250 cc saline The catheter was rted transurethrally until the two micro transducers within the bladder and then attached to the steering of the apparatus with the aid of a clamp To test this tion the patient was requested to cough During this it was also checked that the transducers transmitted pressure equally (Fig 5) By starting the motor the eter was withdrawn at a constant speed of 3 6 sec In this way the proximal transducer (Fig 1) re ed the intraluminal pressure (Fig 5) at every point 1 the internal to the external meatus of the urethra



4 The whole recording equipment

The distal transducer placed at the tip of the catheter 6 cm from the proximal transducer remained in the bladder Consequently the intravesical and the intraurethral pres sures were recorded simultaneously Since the difference between the pressure signals from the two transducers was amplified and recorded separately on the pressure diagram the closure pressure i e the intraurethral pres sure minus the bladder pressure was obtained throughout the pressure measurement (Figs 3 4 and 5) With the distal transducer still in the bladder the movement of the catheter was reversed recording another profile (Fig 5) This procedure was easily performed without any discom fort to the patient At least three profiles were recorded The values in Tables I and II are mean values in mm from three consecutive measurements in each patient Only curves with obvious artefacts due to cough or other movements were discarded The error of a single determi nation (e) was calculated from the formula (10)

$$e^2 = \frac{\Sigma\Sigma(x_{ij} - X_i)^2}{?n_3}$$

x_{ij}=individual observations for person i X_i=the mean value of three determinations for a given person i n =the number of persons for whom three observations were made

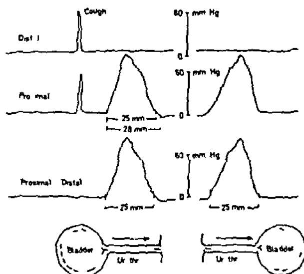


Fig 5 Urethral pressure profile diagram from a healthy woman The curve at the top=the bladder pressure the curve in the middle=the urethral pressure the bottom curve=the closure pressure (urethral pressure minus bladder pressure) To the left both the transducers placed in the bladder A cough indicates equal pressure transmission from both transducers The catheter is then slowly pulled backwards The proximal transducer no 2 is now recording the intraurethral pressure from the inner to the outer meatus=the urethral pressure profile The distal transducer no 1 still in the bladder record at the same time the intravesical pressure The maximal intraurethral pressure amplitude is in this case recorded 11 mm from the inner meatus The functional length of the urethra is 25 mm and the absolute length of the urethra 28 mm When the catheter was inserted a reverse pressure profile was obtained Note that these profiles are identical demonstrating the reproducibility of the present technique

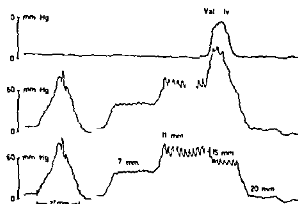


Fig 6 In this diagram the withdrawal was stopped when the proximal transducer was 7 mm 11 mm 15 mm and 20 mm from the internal meatus Note that when the proximal microtransducer was stopped at the maximal urethral pressure point of marked pulse waves were recorded In this healthy woman a Valsalva manoeuvre did not influence the closure pressure as shown in the bottom curve

MATERIAL

Twenty five women volunteers were examined by the technique described above All the patients were clinically normal Tables I and II present data of the patients From these tables it can be seen that the patients were divided into two groups (A) postmenopausal women (B) fertile women

RESULTS

From the technical point of view the equipment functioned satisfactorily at all the examinations Static and dynamic calibrations before and after every examination were identical The disinfection seemed to be satisfactory and no urinary infection occurred In all patients urinary cultures before and after the examinations were negative The thin relatively soft catheter was inserted through the urethra without any discomfort to the patient

From the pressure diagram (Fig 5) it can be seen that the intraurethral pressure was re...

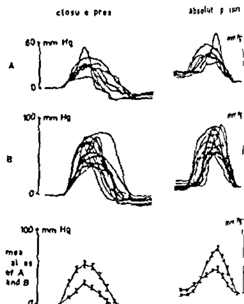


Fig 7 This figure gives the urethral pressure profiles of each of the 25 patients examined The uppermost part of the figure represents the 10 postmenopausal women (group A) the middle part the 15 fertile women (group B) the lower most part of the figure gives the mean values and the standard error of means of group A and B (see also text and Tables I and II The closure pressure and absolute pressure in group A are lower than in group B As can be seen from the definitions the closure pressure is recorded from that point in the urethra where the intraurethral pressure exceeds the intravesical pressure The absolute pressure however is recorded in relation to the atmospheric pressure

e I *Data and results of examinations in 10 healthy postmenopausal women*

functional and absolute lengths the maximal urethral pressure and the bladder pressure are the means of three -vations in each subject Lengths in mm Pressures in mmHg X =mean value S E =standard error of the mean

nt	Age	Child births	Menopause (years)	Functional urethral length	Absolute urethral length	Maximal urethral pressure	Bladder pressure
	63	0	>10	33 0	36 6	61	12
	63	0	>10	24 4	30 9	31	12
	69	III	>10	16 6	?2 2	45	9
	64	0	>10	?3 0	?9 6	39	10
	63	II	>10	15 5	?2 9	29	14
	57	II	4	27 0	31 9	50	14
	74	I	>10	14 7	21 8	63	17
	64	II	>10	?3 8	30 6	37	10
	78	I	>10	23 1	31 8	40	14
	58	III	8	27 6	31 8	40	10
	65 3	1 4		22 9	29 0	43 6	12 2
	2 1			1 0	0 9	2 1	0 8

ltaneously with the bladder pressure The r most curve of this diagram shows the closure ure At the right side of Fig 5 the reproducibil f the recording technique is demonstrated The ure diagram (Fig 6) shows that the catheter be stopped at any time during the withdrawal dure which gives an opportunity of studying ressure at any part of the urethra in detail over nger period of time As seen in Fig 6 the ter was stopped when the proximal transducer in front of at and behind the point of maximal intraluminal pressure Note the distinct pulse waves which had their highest amplitude at the point where the maximal urethra pressure was recorded The length of the urethra can be calculated if the withdrawal rate and the speed of the recording paper are known In Fig 5 the functional length of the urethra was 25 mm and the absolute length was 28 mm In Fig 6 the functional length was 21 mm

The result of the measurements of the urethra pressure profile in the 25 patients is presented in Tables I and II and Fig 7 From these it can be

II *Data and results of examinations in 15 healthy fertile women (group B)*

functional and ab olute lengths the maximal urethral pressure and the bladder pressure are the means of three vations in each subject Lengths in mm Pressures in mmHg X =mean value S E =standard error of the mean

nt	Age	Child births	Functional urethral length	Absolute urethral length	Maximal urethral pressure	Bladder pressure
	15	0	19 3	23 3	67	6
	4?	0	26 1	27 6	45	9
	30	I	31 1	34 7	46	5
	28	II	?8 7	29 7	75	4
	30	0	32 7	35 4	67	5
	?8	II	?2 3	25 3	61	6
	4?	I	26 ?	32 6	57	11
	3?	III	25 0	29 1	87	5
	30	III	25 0	29 2	66	9
	30	II	2? 2	26 1	68	10
	?8	0	31 3	32 9	95	3
	8	II	?6 0	29 6	78	4
	39	II	?6 2	30 3	52	6
	13	0	24 5	27 9	69	7
	30	I	?6 0	29 5	70	10
	?9 7	1 3	26 2	29 6	66 5	6 7
	? 1		0 6	0 5	2 3	0 7

clearly seen that the postmenopausal women (group A) had a significantly lower maximal urethral pressure than the fertile women (group B) The mean maximal urethral pressure was 42 6 mmHg (group A) and 67 7 mmHg (group B) ($p<0\ 001$) The elderly patients had a significantly higher bladder pressure at rest than the younger women 12 2 mmHg and 6 7 mmHg respectively ($P<0\ 001$) No significant difference was noted in the absolute length of the urethra between the two groups 29 0 and 29 6 mmHg respectively The functional length of the urethra was 22 9 mm in group B and 26 2 mm in group A This difference is statistically significant ($P<0\ 01$) but should be judged on the basis of the significantly higher intravesical pressure in group A

The functional and absolute length showed a significant difference in each group ($P<0\ 01$) The parity of the two groups was identical (Tables I and II)

DISCUSSION

As was discussed in the introduction reliable measurements of urethral pressure can provide excellent information about the function of the urethra especially if the intraurethral pressure is measured at the same time as the intravesical pressure (3 5) It was stated that the following measurements of the urethra should be determined The absolute length the functional length the localization and the amplitude of the maximal intraluminal pressure at rest

The length of the urethra is considered to be of great importance in the maintenance of continence (8) Localization of the site where the maximal urethral pressure is present at rest is very important because the urethra exerts its maximal sphincter function at this point Within this area or at this point the influence on the urethral sphincter exerted by different drugs ought to be tested By the same token this part of the urethra should be investigated with uro dynamic tests in cases of stress urinary incontinence Furthermore by observing the presence of pulse waves within this area our conception of the vascular and general condition of the urethra as well as the importance of the vascular bed for the maintenance of continence can be improved (5)

The results of the examinations in the 25 patients with the aid of our new technique showed that it was possible to make these measurement urethra with a high degree of precision

As can be seen in Tables I and II the functi length as well as the absolute length of the ure could be reproduced with an error of less than I (e =0 49 and 0 71) From Fig 6 it can also be that the maximal intraluminal pressure at rest be determined with great accuracy both as re the localization in the urethra and as regards magnitude of its pressure amplitude The re pulse waves had their highest amplitudes in area of the urethra where the maximal pres was present

Tables I and II and Fig 7 show that the max urethral pressure at rest decreased with increa age This observation is in accordance with re published by Enhorning (5) Urethral functio consequently also the urethral pressure profile be impaired due to damage resulting from (5 7) However in our investigation the parit the same in the two groups examined (Tables I II) Therefore the influence of this factor on urethral pressure profile ought to be the sa both groups of patients Whether the deficies estrogens in the postmenopausal women wa cause of their low maximal urethral pressure a (Tables I and II and Fig 7) is yet to be pr Preliminary results of examinations of menopausal women with low urethral pre show that the urethral pressure at rest incre after administration of large doses of estr (Asmussen & Ulmsten to be published)

The urethral pressure profile might eve during the different phases of the menstrual c Therefore we examined the fertile women 6-8 after the first day of the last period

The present study was carried out on a sel number of patients For this reason the biol conclusions should be drawn with some ca Our intention was mainly to perform a method ical study employing a new clinically useful nique capable of accurate measurements of urethral pressure profile Evidently this tec has several advantages over previous methods it is not impaired by the risk of measuring art induced in fluid filled open-end catheter reco systems (1) (B) the frequency response of the cording system is more than 2000 Hz which above that needed for reliable recording of the sure variations in the lower urinary tract A implies a standardized simple and reliable

of the whole measuring system including ltaneous disinfection of the recording catheter ı small active measuring surface of the micro ·ansducer (0 75 mm²) facilitates recording of the luminal pressure at practically every point ın the urethra Therefore accurate determina of the length of the urethra in addition to the ·ızation of the maximal pressure point at rest ɔe performed with a high degreee of precision ·he intraurethral pressure is always measured ltaneously with the intravesical pressure thus losure pressure is recorded at every phase of xamination

l these advantages are obtained without any lvantages to the patient which means that the ·ding catheter is used easily without any risk of ɔmfort to the patient We therefore consider the ·nt technique superior to previously used tech ·s for measuring the urethral pressure profile

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ANNOUNCEMENT

Postdoctoral Fellowships in Andrology Wayne State University School of Medicine has initiated a multidisciplinary postdoctoral training program in andrology at the C S Mott Center for Human Growth and Development (Director T N Evans M D)

Trainees will conduct basic research with clinical orientation in gynecology urology internal medicine pathology immunology or microbiology Research interests include neuroendocrinology of reproduction endocrine profiles tissue culture of testicular biopsy cytochemical pathology of sperm ultrastructural localization of sperm enzymes scanning electron microscopy immunoandrology and bacteriology of the [illegible] Fellows are expected to attend advanced [illegible] Human Reproductive physiology and to [illegible] annual C S Mott Colloquia in Andrology Selec[illegible] applicants is based on previous research exper[illegible] Double qualifications (M D & Ph D or D [illegible] Ph D) are preferred Deadline for application [illegible] 1976 For information and application forms [illegible] Director of Postdoctoral Training Dr E S E H[illegible] Reproductive Physiology Laboratories C S Mott [illegible] for Human Growth and Development Wayne S[illegible] University School of Medicine Detroit Michigan [illegible]

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SHORT COMMUNICATION

PLASMA RENIN ACTIVITY IN ABORTION

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ract Healthy women (N = 96) were investigated for ges in plasma renin activity (PRA) in abortion In taneous abortion PRA levels were significantly lower in induced abortion although higher than in healthy en These findings may be explained by differences in is luteum function and renin production of the feto-ntal unit. Alternatively prostaglandins released by ontracting uterus in spontaneous abortion may cause suppression as observed in 9 pregnant women with ion induced by the intra amniotic use of prosta-lin $F_{2\alpha}$

e is known about the role of renin in pregnancy labour in humans It has been reported that ma renin activity rises during pregnancy (4 6 l 14) and falls nearly to normal approximately ours after parturition (1 7 9) It has also been vn that plasma renin concentration is raised g highest during the first trimester of preg y having a tendency to fall towards term (7 8) ough all these factors are increased during nancy the importance of this finding is not wn To investigate the possible role of renin in arriage mothers with both spontaneous and ced abortion were studied for the changes in plasma renin activity and compared with hers with uncomplicated pregnancy

MATERIAL AND METHODS

ty six healthy pregnant women aged 17–4? years no previous history of renal or vascular disturbances investigated None of them showed hypertension or retention Twenty-six subjects had a spontaneous tion at 9–13 weeks of gestation The abortions were pleted by evacuation and curettage Twenty six sub were taken into the hospital for threatened abortion at 8–20 weeks of gestation but did not abort and later had normal deliveries Thirty six subjects were normal con trol at 10–40 weeks of gestation The microscopy of the spontaneous abortions showed no histological abnormalities All the subjects were on their normal home diet

The blood samples for measuring plasma renin activity were collected the first day the subject came to the clini and the day following the abortion The control samples were taken during the subjects normal visits to the clinic All samples were taken after 20 minutes supine position after 12 hours of fasting at 10–11 a m Diet was un restricted Plasma renin activity was measured by a radio-immunoassay method (3 4)

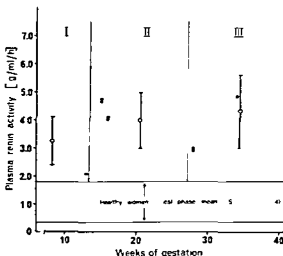


Fig 1 Plasma renin activity in healthy pregnant women (N = 36) throughout pregnancy The roman numbers indi cate the trimesters For each trimester the mean±S D is indicated with open circles and bars Reference values of healthy women in the luteal phase are also indicated

Table I *Plasma renin activity in spontaneous and induced abortion in healthy women compared to no… pregnancy and non pregnant women*

Group investigated	N	Week of gestation	PRA mean±S E M (ng/ml/hr) Before abortion	After abortion
1 Spontaneous abortion	10	9–13	2 42±0 44	2 08±0 36
2 Induced abortion	26	8–16	4 54±0 43	5 27±0 39
3 Threatened abortion	26	8–20	4 52±0 39	
4 Normal pregnancy	20	10–20	3 86±0 24	
5 Non pregnant estrogen phase	37		0 74±0 08	
6 Non pregnant luteal phase	34		1 18±0 13	

Significances of differences obtained with Student s *t* test
Group 1 before/after $p<0\ 5$ N S
Group 2 before/after $p<0\ 2$ N S
Group 1 before/group 2 before $p<0\ 01$
Group 1 after/group 2 after $p<0\ 001$
Group 1 before/group 3 $p<0\ 005$
Group 1 before/group 4 $p<0\ 01$
Group 1 before/group 6 $p<0\ 001$

RESULTS

During normal pregnancy plasma renin activity rose showing a slight increase towards term (Fig 1) The level of plasma renin activity in subjects admitted to the clinic for induced abortion did not differ from the level in subjects coming because of threatened abortions which never occurred whereas the level of plasma renin activity in subjects with spontaneous abortion was significantly lower (Table I) Plasma renin activity before abortion did not significantly differ from the level after abortion

DISCUSSION

The observation of raised plasma renin activity during pregnancy slightly increasing towards term agrees with previous reports (5 7 8 11 14) Plasma renin activity in subjects admitted to the clinic for induced or threatened abortion appeared to be quite comparable to the normal control material thus only showing the rise normally observed in pregnancy On the contrary subjects having a spontaneous abortion showed a significantly lower plasma renin activity being only slightly elevated compared with healthy non pregnant women (Table I) The microscopical findings of the fetuses did not explain the abortions The possible mechanisms could thus have been hormonal insufficiency or blighted ovum

Estrogens are known to increase renin substrate by stimulating syntehsis in the liver (6) which has been assumed to cause the raised levels of plasma substrate in pregnancy Progesterone is thought to increase plasma renin activity through aldosterone antagonizing effect (10) It is pos… than an inadequate secretion of these hormon… partly the cause of the lower plasma renin ac… levels observed

Renin activity is increased in amniotic flu… and it has been shown that renin is secreted b… chorionic cells of the placenta (12) It is pos… therefore that part of the renin in maternal cir… tion is derived from the feto placental unit a… been speculated (1 8 9) However chorionic… is presumed to be inactive unless exposed at… stage to pH 3 to 4 (12) In the present metho… PRA measurement (3 4) pH of plasma samples… kept at 6 0 Thus chorionic renin was not mea… unless some unknown physiological activators… present In the cases supposed to be caused… blighted ovum the growth of the feto-plac… unit is disturbed It can be assumed also th… capability to secret renin is diminished

It is difficult to state the exact time for abor…

Table II *Plasma renin activity in 9 pre… women before and after legal abortion in… with prostaglandin $F_{2\alpha}$ (PGF)*

Sample	N	Week of gestation	PRA mean±S… (ng/ml/hr…)
Before PGF	9	8–12	3 19+0 …
2 hours after PGF	9	8–12	1 88+0 …

Prostaglandin $F_{2\alpha}$ 50 mg was administered … amniotically
* Significance of the decrease obtained with Stud… *t* test $p<0\ 01$

cases of spontaneous abortions In some pa its abortion had possibly taken place before mission to the hospital although the feto ntal unit still remained in the uterine cavity In h cases the whole organism probably no longer ed as in pregnancy and consequently plasma in activity was decreasing

t could not be shown that the low plasma renin ivity was responsible for spontaneous abortion nay instead have been a sign of inappropriate duction of estrogen and progesterone or ormalities in the evolution of the feto placental it Low plasma renin activity during the first tri ster of pregnancy seems to indicate an increased of spontaneous abortion

ecently our attention was drawn to a report on eased plasma progesterone and oestradiol levels premature labour (13) If these observations ap to patients with spontaneous abortion and a th of gestation comparable to that of our pa ts our observation of low plasma renin activity pontaneous abortion cannot be explained by low duction of progesterone or oestradiol

'e have recently observed suppression of ma renin activity in abortion induced by the a uterine injection of prostaglandin $F_{2\alpha}$ 50 mg ble II) It may be assumed therefore that ma renin activity is suppressed in spontaneous rtion by prostaglandins released by the contract uterus into the blood stream Suppression of ma renin activity may offer a new basis for dicting prognosis in threatened abortion

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CASE REPORTS

CONGENITAL ANNULAR CONSTRICTIONS DUE TO AMNIOTIC BANDS

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tract Amniotic bands which become involved with l parts especially the extremities are producd by ure of the amnion during pregnancy with the conse nt union of the extra embryonic mesoderm in fibrous igs An infant with the amniotic band syndrome in m an annular constriction of the left leg and right hand found is described He was treated successfully by tiple Z plasties and a plaster cast to correct the foot The oedema of the leg persisted for 5 weeks and ı subsided completely The role of amniotic ab- nalities in the production of congenital malforma s is reappraised The microscopic and histological in igation of the placenta and membranes should ac pany every case of fetal malformation in abortuses births and affected newborn

iough congenital fetal anomalies associated with ormalities of the fetal membranes have been ribed in the literature for more than 300 years e is still some doubt that they are etiologically ted (Willis 1962 Streeter 1930) According to pin (1968) the amnion may rupture during gesta and the extra embryonic mesoderm together ı the separated amnion may form fibrous ds Various fetal structures such as the ex nities or the umbilical cord may be entangled ilting in the production of annular constriction mputations If the umbilical cord is constricted l death will result

he present report is of an infant with amniotic ȝ syndrome suffering from congenital annular trictions of the left leg and the right hand h were treated successfully

CASE REPORT

ıf a 22 year-old primigravida was admitted to the ery room in her 39th week of pregnancy Her antenatal course had been uneventful and except for vita min and iron supplements for prevention of anemia no medication had been administered Her blood group was B Rh positive On examination the abdomen cor responded to the gestational age the fetal heart beats was normal the cervix was dilated 2 cm and the amniotic sac was ruptured The delivery was uneventful except for somewhat slow progress (15 hours from the time of arri val) for which an oxytocin drip was given at 7 cm dilata tion of the cervix

A male weighing 3 000 g was born with an Apgar score of 10 after one minute The placenta was expelled 3 min utes later On examination the placenta appeared nor mal though a band of dense tissue was found to emerge from the fetal surface of the placenta This band sur rounded the umbilical cord near its attachment to the placenta The histological examination of the band showed dense connective tissue which was found in some areas (Fig 1) to be necrotic The dense tissue was covered by amniotic epithelium

Examination of the infant revealed a gestational age of 42 weeks On the left lower leg immediately above the ankle a deep circular constriction was found The skin and soft tissue was absent and the tibia and fibula were exposed The left foot was completely flail and showed marked clubbing (Fig ?) as well as severe oedema distal to the constriction The skin on the leg was warm The nail and the third phalange of the second and the third fingers on the right hand were missing The skin over the palm and fingers was wrinkled Radiographic examination showed a mild deformity of the distal part of the left tibia and fibula The distal phalanges of the second and third fingers of the right hand were absent No other anomalies were observed

The child was operated on at the age of one day Under tourniquet control the medial half of the constriction was excised down to the bone and no muscles or tendons could be identified Skin and subcutaneous tissue were sutured by multiple Z plasties and the leg put into a plaster cast to correct the clubfoot The would healed satisfactorily and oedema decreased steadily Three weeks later the re maining half of the annular constriction was operated on in a similar fashion After excision of the constricted area a



Fig 1 A band of dense tissue emerging from the fetal surface of the placenta

considerable amount of clear oedematous fluid gushed out from the wound edges Again no muscles or tendons could be detected

The postoperative course was uneventful and at the end of 2 weeks the oedema of the foot had almost completely subsided

DISCUSSION

The formation of amniotic bands and the entanglement of various parts of the fetus especially the extremities with consequent developmental deformities of the fetus are ascribed to the complete or the partial separation of the amnion from the chorion The spectrum of the deformities varies from minor defects such as syndactyly to complete amputation of a limb or even fetal death due to constriction of the umbilical cord

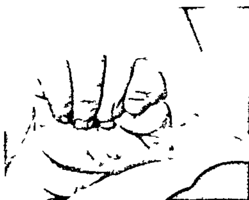
According to Streeter (1930) amniotic bands are due to developmental defects occurring at the formation of the germ disc and the fetal membranes Imperfect development leads to a localized sclerosis and sloughing off the tissue which in formation of fibrous bands Torpin (I gested that amniotic bands arise from rupture of the amnion without injury of the Fibrous bands are found on the detached and the chorion Protruding fetal parts such gers and limbs may be entrapped by the gradually become constricted and even

In addition absorption of amniotic fluid by amnion denuded chorion may occur and con to the triad of defects associated with amn bands intra uterine amputations clubbing of feet and lymphedema distal to the side of cons tion The absence of the third phalange and third finger of the right hand only in our case can be explained by an early amputation probably d to the same cause as the annular constriction of leg namely amniotic bands Syndactyly and amputations of fingers due to amniotic bands have reported in a human fetus at an age as early as weeks (Ornoy et al 1974)

Congenital annular constrictions are con niently classified into five degrees of severity Only a shallow groove is present which us requires no treatment (2) The groove is deeper encroaches to a varying extent on subcutan tissues or muscles function is usually normal The constricting band deepens to the bone Oe of varying degree is present distal to the cons tion as an expression of impaired venou lymphatic return Sensation may be disturbed if the band is on the leg clubfoot is usually p (4) Symptoms are the same as in (3) but s addition pseudarthrosis of the bones tibia or and fibula (5) Intra uterine amputation



Fig 2 A deep circular constriction is seen on the lower leg with clubbing and edema of the leg



l The nail and the third phalange of the second and finger of the right hand are missing

ı interesting question ıs how the part distal to onstriction gets its blood supply in degrees (3) (4) Stevenson (1946) postulated blood supply ıgh the bones although it seems more probable collateral circulation is established through hes of the peroneal and anterior tibial vessels h in their distal parts lie immediately over the s and the interosseous membrane

veral cases of amniotic band deformities have reported in children born to mothers who have ı L S D (lysergic acid diethylmide) (Zellveger 1967) Although Tjio et al (1969) could not lefinite evidence to prove that L S D damages ın chromosome chromosome aberrations have described in human fetuses which have been sed to L S D in utero

our case a normal chromosomal karyotype 46 vas found

ı antivitamin compound Citral when injected ı 3-day-old chick embryo was found to induce nital malformations some of them associated amniotic fibrous bands and adhesions be n the amnion and the embryo (Abramovici The teratogenic mechanism appears to be a effect of Citral that acts simultaneously on yonic tissue and the adjacent area of yonic membranes

grees (4) and (5) of the congenital annular con ion require early surgical treatment to improve lation and to reduce the oedema which in might become so severe as to obstruct the mical features of the affected extremity standing edema may lead to induration infec ınd gangrene

ter excision of the constricted ring the skin and soft tissue are united in zig zag fashion by rotat ing multiple local triangular flaps into the suture line (multiple Z plasties) thus avoiding a long straight scar which by postoperative constriction could recreate the original constriction

With constriction degrees (3) and (4) the opera tion is done in two stages with an interval of sev eral weeks so as not to compromise the already precarious blood supply to the distal part Thus the operation reduces considerably the distal oede ma or even eliminates it completely Additional orthopedic procedures are required to treat the clubfoot (casts tendon lengthening arthrodesis)

After the reduction of the oedema by Z plasties the degree of sensory disturbance usually de termines the ultimate fate of the affected part since a completely anesthetic foot is prone to repeated ulceration infection and might eventually require amputation

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VAGINAL SURGICAL INTERVENTION FOR A SACRO COCCYGEAL TERATOMA OBSTRUCTING LABOR

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ract Congenital sacro-coccygeal teratomas are rare ɔrs and may cause dystocia The case presented was aged unusually by incisional drainage of the tumor ugh the vagina in a course of an obstructed labor gh the vaginal delivery resulted in the birth of a live .hy infant

tocia may be due to many maternal and fetal ors The common fetal factors in dystocia are ormal presentation large size deformities and ors Few cases of fetal sacro-coccygeal tera a causing a severe degree of obstruction to nal delivery have been reported In most of the s the newborn was lost during or soon after the ative delivery (1 6 7) The following report is pecial interest because of the unusual manage t applied during the course of an obstructed r caused by a huge sacro coccygeal teratoma the favorable results obtained

CASE HISTORY

patient Y S 23 year-old primigravida was admit o the delivery unit in active labor in her 8th month prenatal course was uneventful except for the fact since the seventh month of pregnancy the uterus was ously larger than was expected On admission clini valuation of the patient estimated the fetus at term although the patient was at 35 weeks by dates Her l pressure was 140/80 mmHg There was no oedema buminuria The fetal heart rate was regular 150 beats minute The cervix was fully effaced and dilated to 4 The fetal head was at zero station The membranes intact An X ray film was done because of the suspi of twins or hydramnios and showed a normal-looking in cephalic presentation and no evidence of cephalo-pelvic disproportion There were no signs of hydramnios Amniotomy was performed and labor prog ressed normally A right mediolateral episiotomy was done and the head arms and thorax were easily delivered At this stage the delivery came to a standstill and the abdomen buttocks and legs could not be delivered although abdominal pressure associated with traction was applied

Palpation within the uterus revealed a very large soft tumor with broad attachment to the buttocks of the fetus During this period the infant was breathing and grimacing The air passages were sucked out and oxygen was given constantly to the half born infant The patient was im mediately anaesthetized and long scissors were intro duced through the vagina above the infant s back into the lower uterine segment and an incision was made on the surface of the tumor Clear fluid was released Im mediately after this procedure and with the assistance of strong fundal pressure and firm traction of the infant s chest a female weighing 2 860 g with a partially collapsed sacro-coccygeal teratoma was extracted The Apgar score at 1 minute was 5 and at 5 minutes 9 The third stage wsas normal The incision in the tumor was sutured and the infant was transferred to the newborn unit Under general anaesthesia examination of the uterine cavity was performed and the episiotomy was sutured

Twelve hours later the infant was transferred to the Department of Pediatric Surgery On examination no abnormalities were found except for the mass on the but tocks This mass was attached to the coccyx and sacrum measured $25 \times 20 \times 20$ cm (Fig 1) and a large 10 cm sutured incision on the posterolateral surface could be seen Most of it was cystic except for a thick cord attached to the vertebral column The anal area was distorted and marked posterior compression of the recto sigmoid colon was felt on rectal examination Straight X ray films of the baby revealed calcification in the mass Barium enema showed posterior compression of the rectum and part of the sigmoid colon On I V P moderate bilateral hydronephrosis and hydroureters with excellent excretion from both kidneys were visible Laboratory examinations



Fig 1 Sacro-coccygeal teratoma partially collapsed immediately after delivery

revealed slight anemia and the blood urea nitrogen electrolytes liver function tests and blood gases were normal

The infant was prepared for surgical intervention during the following twelve hours with systemic antibiotics and rectal irrigations Surgery was performed with the baby in jack knife position Through an inverted V incision the coccyx was excised and the middle sacral vessels ligated and divided The tumor was removed from the rectosigmoid wall and the retroperitoneal area by blunt and sharp dissection Special attention was paid not to injure the bowel the pudendal and sciatic nerves A part of the gluteus maximus muscle on both sides had to be removed with the tumor Following complete excision the wound was closed and drained The tumor weighed 460 g and microscopic examination confirmed the diagnosis of benign sacro-coccygeal teratoma

Postoperative recovery was uneventful and the surgical wound healed well and with a good cosmetic result (Fig 2) No neurological deficits could be detected The baby was ready for discharge ten days postoperatively but a severe Escherichia coli urinary infection occurred Aggressive antibiotic and supportive therapy together with bladder drainage at later stage could not control the infection and the baby died on the 37th postoperative day from sepsis Permission for performing a postmortem was not granted by the family

DISCUSSION

Congenital tumors of the sacro-coccygeal region occur every 1 35000 to 40000 births (9 10) Sacro-coccygeal teratomas make up a small fraction of those and only a small number will cause obstruction at delivery (9) It has been estimated that dystocia may occur in 6 0 to 11 7% of cases (4 11) In such cases the teratomas are large at b[illegible] measuring 15–20 cm or more in diameter

There are many theories to explain the or[illegible] sacro-coccygeal teratomas Gross et al (3) b[illegible] that they originate early in intrauterine life f[illegible] pluripotent or totipotent primordial cells The[illegible] cur with greater frequency in the areas where greatest concentration of primitive cells exist[illegible] *the longest period of time e g in the pr[illegible]* knot (Hensen s node) near the coccyx an[illegible] reproductive gland anlage

Sacro-coccygeal teratomas which occur [illegible]minantly in female infants (3 4 11) contain [illegible]nents of all three germ layers may be cystic [illegible] and are usually surrounded by a dense caps[illegible] The potential for even apparently [illegible] sacro-coccygeal teratomas to undergo m[illegible] changes has been demonstrated (4) The m[illegible] transformation occurs after 4 months of life [illegible] total removal of the teratoma immediatel[illegible] birth is necessary and the infants tolerate th[illegible]tion very well (9)

Prenatal diagnosis of sacro-coccygeal te[illegible] is unusual *They are mostly diagnosed after* [illegible] cases of premature delivery with small tu[illegible] when obstruction at delivery occurs (?) P[illegible] plain radiographs rarely incite diagnostic s[illegible] that these tumors may be present (8) [illegible] amniography is done



Fig 2 The anal region after surgery

all tumors may be delivered vaginally by firm on (5) but in cases of large tumors otomy may be required (4) In most of the ted cases where obstruction at delivery oc d and operative delivery was performed ei vaginally or more often abdominally the in were lost during or soon after the procedure rted attempts to drain the teratomas with a e in the course of an obstructed labor or to ct the tumor blindly from the fetus through the a failed either because no fluid was obtained cause of the high location of the tumor within terine cavity (1 2 6) In those cases it was ssary to perform hysterotomy and to excise or the tumor before vaginal delivery could be oleted

most cases of sacro-coccygeal teratomas *h are not diagnosed prior to delivery and which* uct labor abdominal delivery ends in in rtum death Therefore we would like to sug that a large incisional drainage of the tumor enable vaginal delivery while resuscitative ures are being taken and may lead to some atal salvage

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LETTER TO THE EDITOR

CONGENITAL MALFORMATIONS AND DECREASED BLOOD LEVEL OF FOLIC ACID INDUCED BY ANTIEPII EPTIC DRUGS

Sir

e are a few diseases e g epilepsy for which amounts of drugs are taken Anticonvulsive cross the placenta and the fetuses of women ich therapy are exposed to these drugs during entire gestation (1 2)

rious studies have shown differing degrees of genicity associated with anti epileptic drugs we & Van Eck (3) found that the frequency of rmations in children born to mothers under otic treatment was eight times greater than in a ol group Speidel & Meadow (4) and Lowe (5) l a frequency of malformations 2–3 times r than in epileptic mothers who did not take onvulsive drugs or in the general population ongenital malformations are attributed to the hat barbiturates and diphenylhydantoin de e the blood level of folic acid by inducing an se in microsomal enzymes which accelerate etabolism of folic acid (6) It is known that low of folic acid in mother s blood are associated ongenital malformations and mental retarda 7)

etrospective study was conducted to deter the frequency of malformations among new nfants of 70 mothers who received anti tic drugs during pregnancy (8) Of 56 births dren were born with malformations an inci of 16% Four children were born dead or hortly after delivery Congenital heart disease p with or without cleft palate neural tube de and skeleton abnormalities were the com t anomalies found

folic acid level of two women suffering from mal epilepsy was measured in the seventh of their first pregnancy Both women had re l anti-convulsant therapy for a number of One received trimethadione 1 2 g daily di thydantoin 0 3 g daily and primidone 1 g dai e second received diphenylhydantoin 0 4 g and phenobarbital 60 mg daily Their blood cid levels were 55 mg/ml whole blood and 70 ng/ml whole blood respectively (normal range 130–200 ng/ml whole blood) The first woman delivered spontaneously in the 7th month a 1 700 g male infant with anencephalus cleft lip and palate The infant died within two hour The second woman de livered at term a 2800 g male infant with hypo spadias

Anti-epileptic drugs are as necessary to a mother s health during her pregnancy as they are prior to it It is therefore recommended that women receiving anti epileptic therapy be given supplemental folic acid and their folic acid and their folic acid level monitored

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Acta Obstet Gynecol Scand 55 188–190 1976

LETTERS TO THE EDITOR

The following letter has been received from doctors Kivikoski and Pulkkinen in Turku Finland As many of our readers probably know there is still much discussion concerning the role of progesterone for the preservation of pregnancy in women At the Sabbatsberg Department of Obstetrics and Gynaecology we had a case two years ago where the corpus luteum of pregnancy had been extirpated on the 26th day of the menstrual cycle and the patient had a full term delivery in spite of the fact that no hormonal treatment had been given during the pregnancy

The polemical formulation of the letter is the authors own responsibility

Axel Ingelman Sundberg
Chief Editor

Dear Sir

The article Serum Levels of Oestradiol and Progesterone during Administration of Prostaglandin F2α for Induction of Abortion and Labour by O Widholm P Kajanoja and E D B Johansson (Acta Obstet Gynecol *54* 135 1975) presents no new factual data and therefore deserves no comment However the acceptance of this manuscript for publication by the Acta Obstet Gynecol Scand does demand considerations For this article has been published in spite of the authors

(1) conclusion that the action of prostaglandin F2α on the myometrium does not appear to be mediated through changes in progesterone (or estrogen) levels when their *own* data showed statistically significant progesterone withdrawal (Pw) preceding prostaglandin (PG) induced abortion every time the number of study patients within the group was at least 10

(2) comment that the PG provoked hormonal changes were less pronounced in the period between the 10th and 14th weeks compared with the second half of pregnancy For their own data show the exact opposite e g 61% Pw at 10–14 weeks 53% at 15–19 weeks and 26% at 36–44 weeks (all of these Pw s being statistically significant) In view of the author s factual data comment is inexcusable What makes it worse is their subsequent statement that during this period the corpus luteum is still functional and tributes to the plasma levels of progesterone obvious but unjustifiable effort to substant earlier study of Holmdahl Johansson & Wide (Endocrinol 67 353 1971) For the cold re (based on 65 cases of luteectomy) that the corpus luteum becomes dispensable during the 7th week of pregnancy (Nagele) due to the luteo placental shift in P biosynthesis (Csapo et al Am J Obstet Gynecol *112* 1061 1972 *115* 1973 *117* 987 1973 Prostaglandins 4 421 Am J Obstet Gynecol *118* 985 1974)

(3) reference to the paper of Tyack et al as taining an argument rather than definitive supportive evidence for the earlier demonstration that hypertonic saline treatment provokes Pw before inducing clinical abortion (Csapo et al Am J Obstet Gynecol *105* 1132 1969 and Wiest et al Clin Endocrinol *30* 774 1970)

(4) manipulation of historic sequence by placing the paper of Holmdahl Johansson and Wide (1971) *after* that of Tyack et al (1973) In so doing the authors could say it now appears that decreased levels of progesterone found before expulsion of the fetus are not significantly related with the onset of clinical labour when the Tyack paper (written *after* the Holmdahl paper) brought out all the significant facts which Holmdahl et al

(5) omission of the massive evidence that precedes PG induced abortion and that the absence of Pw signals treatment failure (Csapo et al Prostaglandins 2 125 1972 Csapo Pros 3 245 1973 Saldana et al Prostaglandins 1973 Enkola Prostaglandins *5* *115* 1974 & Rauramo Prostaglandins *5* *269* 1974 al J Obstet Gynaecol Br Comm *81* 1974 tan et al Prostaglandins *6* *711* 1974 Obstet Gynecol *44* 135 1974 International Conference on Prostaglandins Florence May

—Abstracts Craft & Youssefnejadian Lau et al Ylikorkala et al Aleem et al Schul et al Brenner et al Robbins & Mann)
ıe Editors probably adhere to the principle that ontent of an article published in the Journal is uthors responsibility However it would now ı that not all authors accept this responsibility

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ıder

Sir

ıtter to the Editor by Drs Kivikoski and Pulk concerning our paper Serum levels of oes l and progesterone during administration of ıglandin $F_{2\alpha}$ for induction of abortion and r" (Acta Obstet Gynecol Scand *54* 135 1975) ms the old truth that when logic arguments ıcking emotions are used We would like to our views to the five comments made by Drs oski and Pulkkinen

Everyone working with the endocrinology of ancy appears to agree upon the observed ımena that progesterone levels decrease be arturition This by no means implies that this sterone decrease is the driving force behind ıntractions It appears more likely that it is a quence of the contractions Also in our study ostaglandin induced labour and abortions terone and oestrogen levels did decrease be ıe actual abortion or delivery In our opinion due to the myometrial contractions and is not ssity for the action of the administered pros dins

n order to be able to ascertain the activity of rpus luteum the only two samples that can be ıred are samples two and three Sample two is at the expulsion of the fetus with the placenta mple three taken 24 hours later During this ur period the contribution of the corpus still remaining in the ovary will have a to influence the plasma level of progester asur d 24 hours after the placenta has been ed During weeks 10–14 14% of the proges level at expulsion of the fetus and placenta was still remaining 24 hours later At 15–19 weeks 10% at 20–29 weeks 6% and at 36–44 weeks 4% was remaining These figures point to an extra pla cental contribution of progesterone during the early part of pregnancy These findings agree quite well with our previous study (Holmdahl Johansson and Wide Acta Endocrinol *67* 353 1971) but they do *not contradict the findings based on 65 cases of* luteectomy that corpus luteum is dispensable during the 7th to 9th week of pregnancy The myometrium appears to have a low threshold for its progesterone requirements The findings that the corpus luteum can be dispensed with during early pregnancy do not indicate absence of its ability to produce and secrete progesterone Numerous reports show that in fact it appears to maintain that ability throughout pregnancy

3 We still maintain that available evidence points strongly to the release of prostaglandin by hypertonic saline infusion either by intra or extra amniotic injection (Gustavi B Acta Obstet Gynecol Scand Suppl *25* 1973)

The argument under 4 and 5 is then again back to the question which comes first the egg or the hen We still maintain that there is not enough evidence to show that a progesterone decrease precedes the onset of myometrical contractions The long list of references that Kivikoski and Pulkkinen use to show that a decrease in progesterone signals failure of prostaglandin induced abortion is correct but then again high progesterone levels in this setting only indicate that the myometrial contraction has not started

Let us make one point perfectly clear The pro gesterone withdrawal appears to be essential in several species Even we have shown that for in stance in the cow (Edqvist et al Acta Endocrinol *71* 731 1972) and it may even occur in the rhesus monkey (Bosu Johansson and Gemzell Acta En docrinol *74* 743 1973) However it should be un derstood that the situation in women is complex and not altogether parallel to lower animals In women large amounts of progesterone circulate during preg nancy Most of it is bound to transcortin During labour a large amount of the protein bound proges terone is displaced by corticosteroids and the biologically available concentration of progesterone is likely to increase As labour proceeds the pro duction of progesterone is impaired and also the half life of progesterone appears to be increased This is a logical consequence of the increased avail

ability of free progesterone due to the displacement from the binding sites of transcortin The end effect is decreasing levels of total progesterone during labour

As we regard ourselves as humble fellow scientists history may prove us wrong However the other approach of strict adherence to a theory and always to interpret available facts to support this theory without close examination of other alternative possibilities may also turn out to be a mistake We are of course quite convinced that Drs Kivikoski and Pulkkinen will accept the full responsibility of the judgement of history

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PRENATAL DIAGNOSIS OF SOFT TISSUE MALFORMATIONS BY ULTRASOUND AND X RAY

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ract This study presents four cases of fetal soft malformations diagnosed during pregnancy by ultra scanning and amniography The series comprises *fetal teratomas* one case of *fetal ascites* and one of a partial mole with coexistent fetus Diagnostic and ential diagnostic problems are illustrated by a fifth where the final diagnosis was a big maternal ovarian adenoma coexistent with a normal fetus

asonic scanning is a valuable part of examina of pregnant women with reference among r things to fetal malformations For several s it has been possible to diagnose anencephaly hydrocephaly (5 14) and anencephaly is now onstrated as early as in the 17th gestational k (13)

ne recognition of pathologic changes in the first ester such as missed abortion extrauterine nancies and hydatidiform mole has been eved by ultrasonic examinations (4 7)

ne diagnosis of intrauterine organic malforma s is being developed but so far only a few mal ations have been described (6 9 11)

ne soft tissue masses observed by ultrasonic ning may cause differential diagnostic problems their extra or intrauterine site and also as in ast mentioned case whether they are of fetal or ental origin Amniography has in these cases ed out to be an essential supplement to the r examinations (13)

METHODS

equipment used was an Eskoline 20 ultrasonic appa s and a Tektronix 564 storage oscilloscope nniography was performed by ultrasonic guidance insertion of a puncture needle (lumbar cannula 1 2 mm×15 cm) through a puncture transducer (1) As contrast Isopaque (R) 15–70 ml was used The X ray pic tures were taken immediately after the injection and after 24 hours

MATERIAL

The series consists of 5 patients and the indication for the ultrasonic examinations in every case was considerable enlargement of the uterus greater than expected for the gestational age

Case I The patient a 28 year-old woman para 3 in the 19th gestational week was examined by ultrasound because of recurring vaginal bleeding An enlarged uterus consistent with the 28th week and a living fetus in breech presentation were found The biparietal diameter was consistent with a 19 week old pregnancy The rest of the uterine cavity was filled by tissue with mole structure (Figs 1 and 2) Prenatal diagnosis Partial hydatidiform mole with coexistent fetus An induced abortion resulted in the birth of a fetus weighing 281 g The placenta was diffusely affected by hydatidiform change and weighed 707 g Microscopy of placenta demonstrated hydatidiform mole without malignancy

Case II The patient a 21 year-old woman para 1 in the 33rd gestational week was examined by ultrasound be cause of marked hydramnios and preeclampsia Besides hydramnios a big fluid filled cavity was found in the upper part of uterus At first this was interpreted as a hydro-cephalus but an X ray picture showed a cephalic presen tation of fetus without any sign of bony abnormality When studying the ultrasonic pictures again it was ascer tained that the fluid filled cavity described above was fetal ascites (Figs 3 and 4) The patients delivered spon taneously The amount of amniotic fluid was 2600 ml During the delivery the fetal abdomen was punctured and the abdominal cavity contained 1–2 l ascites The infant was dead and weighed 3240 g The placenta weighed 1250 g A chromosome examination of the fetus revealed Down s syndrome

Case III The patient a 33 year-old woman para 2 in the 25th gestational week was examined by ultrasound because of hydramnios The uterus was found to be en

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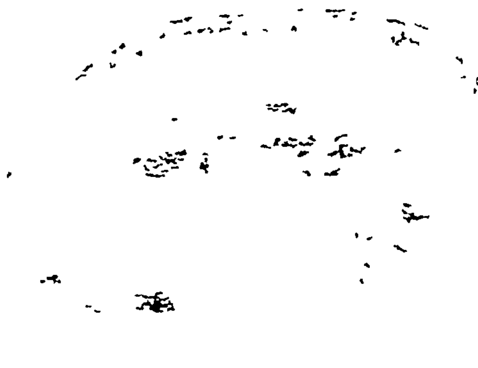


Fig 1 (case I) Transverse scan 4 cm above the umbilicus The fetal head (*arrow*) in the left side of the uterine fundus The rest of the cavity is filled by hydatidiform and hyperplastic placental tissue

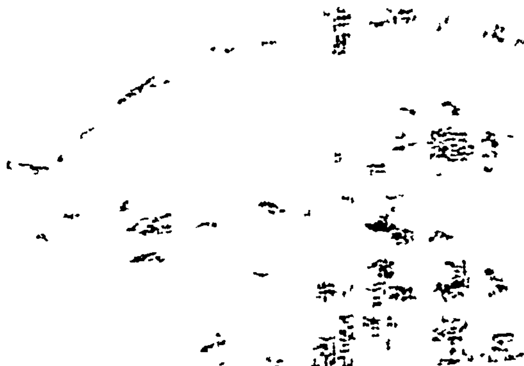


Fig 2 (case I) Longitudinal scan at the midline The uterine cavity is filled by hyperplastic placenta and molar tissue

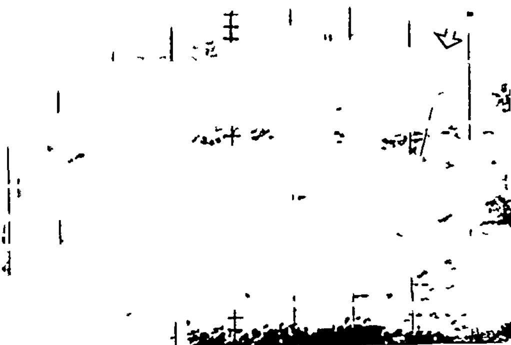
3 (case II) Longitudinal scan to the right of the mid . The fetal abdomen is distended by ascites *A* shows tal diaphragm *B* shows the fetal head surrounded by the arms The head is only scanned partially because of its low presentation

4 (case II) Transverse scan above the umbilicus *A* s the fetal abdomen distended by ascites *B* shows marked hydramnios

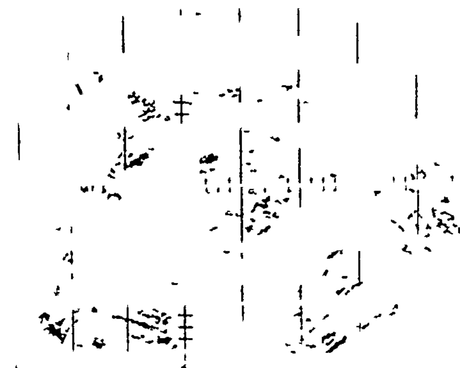
Fig 5 (case III) Longitudinal scan to the right of the mid line *A* shows the head and the fetal body in a low presentation Placenta is located at the uterine posterior wall At the uterine fundus (*B*) is seen a pathologic mass with and without echoes



Fig 6 (case III) Transverse scan above the umbilicus There is a pathologic mass in the uterine fundus



Longitudinal scan to the right of the mid shows the fetal ascites The rest of the cavity is filled by hyperplastic placental tissue and in fundus (*B*) is tumor like tissue



(case IV) Transverse scan at the umbilical plane the hyperplastic placental tissue *B* shows the bdominal tumor tissue



Fig 9 (case IV) The amniography shows a fetus in cephalic presentation In the extension of the vertebral column there is a large area without any contrast (upper 3 arrows) The lower 3 arrows show the outline of the distended body

larged consistent with the 34th week while the biparietal diameter was consistent with the gestational week The diameter of the body was enlarged and there was hydramnios The fundus of uterus was very difficult to scan and suggested a pathologic mass (Figs 5 and 6) The fetus died before further examinations Induction of labor was performed The amount of the amniotic fluid was 1600 ml the head was delivered the body was retained and intrauterine palpation a tumor the size of a coconut was found It arose from the sacral region of the fetus and was adherent to the uterine wall The weight of the fetus was 1700 g The autopsy demonstrated a highly differentiated teratoma arising from the fetal pelvis The placenta was hyperplastic and weighed 1000 g

Case IV The patient a 25 year old woman para 1 in the 26th week was examined by ultrasound because of an enlarged uterus The fetus was a cephalic presentation with a biparietal diameter consistent with the 29th week marked fetal ascites and an intra abdominal mass along the fetal vertebral column was found The uterine cavity was filled by hyperplastic tissue like placental tissue (Figs 7 and 8) The fetal heart sounds were normal The amniography pictures demonstrated a large area without any contrast in the uterine fundus in close relation to the lower part of the fetal vertebral column The fetal body was greatly distended (Fig 9) The prenatal diagnosis was soft tissue malformation of the fetal back ascites and placental hyperplasia The fetal abnormalities were considered lethal and delivery was induced and was terminated vaginally with a dead fetus of 2450 g At autopsy universal edema and 270 ml ascites were found In the sacral region a partially skin covered tumor was found It weighed 512 g The shaped one quarter of it was located with communication through the vertebral 10) Microscopy showed a highly vascularized teratoma The placenta weighed 1000 g

Case V The patient a 30-year-old gestational week was examined by ul an extremely enlarged uterus which ha the previous 2 months A fetus was found presentation without any malformations and parietal diameter consistent with the The fetal heart sounds were normal A large mass surrounded the fetus on three sides seemed edematous or vascular and whether or intrauterine was uncertain (Figs 11 and 1 pictures demonstrated a normal fetal skeleton graphy was made but the contrast was not normal area Labour was induced and ly The infant was normal and weighed 3750 g centa showed no pathologic changes By tion and intrauterine palpation immediately mass of 25×25 cm arising from the left At laparotomy a multilocular cyst arising ovary was found The weight was 17 7 kg (F a pseudomucinous cystadenoma with marked the wall There was very little aqueous fluid in the

DISCUSSION

The prenatal diagnosis of congenital soft formations is important for more than

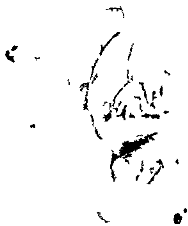


Fig 10 The fetus in case IV

'*1* (case V) Longitudinal scan to the right of umbili
l is the head *B* is tumor tissue

12 (case V) Transverse scan at the umbilical plane
tumor tissue *B* is the fetal body

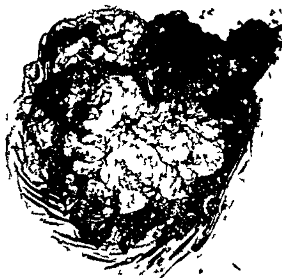


Fig 13 (case V) Pseudomucinous cyst adenoma

In early pregnancy so that induced abortion can be considered and later to avoid fetal and maternal complications during the delivery and if necessary in order to start treatment immediately after the delivery If the malformation is serious the pregnancy may be terminated and thereby spare the mother some psychological trauma If the soft tissue masses is localized outside the uterus it may affect the course of delivery and the treatment of the

A suspicion of hydraminos will often be the reason for performing examinations for possible malformations For this purpose ultrasonic examinations are very suitable because they make it possible to diagnose not only changes on the surface of the fetus but as technique and experience improve also malformations within the fetus (6 9)

In our case (no IV) an intraabdominal tumor was diagnosed in the fetus together with ascites Amniography showed a distended fetal body and also a tumor situated in the uterine fundus connected with the fetal vertebral column The amniography pictures looked like a meningocele but the ultrasonic picture showed a more solid structure like the fetal intra abdominal tumor Case III was a fetal teratoma too in the same position as in case IV—yet the ultrasonic picture was quite different This tumor was less vascular and less edematous In this case amniography was not done because the fetus was dead

Case II demonstrated like case IV the valu of supplementary X ray examination In this c amniography was unnecessary as the must presentation on the ultrasonic scanning was discov ered on the X ray picture and then the correct diag nosis could be made from the ultrasonic pictu In case V the changes were so gross that est part of the tumour were not included ultrasonic picture When trying amniography t contrast was not found through the ma changes By ultrasound we got the inf the pathology was outside the fetus and would obstruct the de ivery In case I the diagnosis of p tial mole was safely made by the ultrasonic exa ination This examination has so far appeared to the most important in the diagnosis of molar dise (2 8 10) It has not previously been possible diagnose a partial mole with coexistent fetus

We have found that tissues of the same his cal structure can result in different ultrasoni p tures when their liquid and solid constituents va On the contrary it can be difficult with ultras to distinguish different histological tissues if th alike in their liquid and solid content and struct Therefore interfaces between two such types of sue can be difficult to scan (Fig 8) Amniogr may be valuable in distinguishing between con ous soft tissue masses within or without the Among the things which do not appear on ultras pictures are the condition of the skeleton and structure and function of the gastrointestinal tr (12 13 15)

Ultrasonic examinations are to be preferred the initial examination because it is without risk produces no side effects The indications of mal an ultrasonic scan for congenital malformations often be as in our cases the suspicion of hyd nios (11) former deliveries of malformed ... and genetic defects in the family It is often ne sary to repeat the examination and have it sup mented by X ray pictures and amniography

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PLACENTO THYROIDAL RELATIONSHIP IN NORMAL PREGNANCY

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ract Estimations of serum HCT HTSH T4 T3 ETR Triosorb TBG binding capacity BMR and ary total estrogen were made simultaneously in 160 nen in normal pregnancy TRH stimulation tests were le in 20 cases in each trimester of pregnancy HCT was ctable even in early pregnancy tending to increase lually toward the terminal stage of pregnancy as serum otrophin bioactivity showed On the other hand se TSH level measured by radio-immunoassay remained ntially the same throughout the course of pregnancy the nonpregnant state moreover it was suggested by TRH stimulation test that pituitary TSH secreting tion of pregnant women was similar to that of the -pregnant These findings suggest that thyroid hyper tion during pregnancy which is shown by progressive creased T3 T4 and PBI may not be due to high ogen high TBG binding capacity low free thyroxine itive feed back high TSH secretion but to HCT origi ng from placenta In spite of thyroid hormone in- se it is true that the clinical picture of hyperthyroid is not manifest among normal pregnant women and t remained within the non-pregnant range throughout course of pregnancy We have also demonstrated that sorb decreased progressively This may be inter ed to be due to the increase of TBG binding capacity h is increased progressively and binds more of free oxine during pregnancy Such a change in TBG ing capacity is well known to be caused by the effect strogen which is progressively increased during preg y In a word it is possible to say that there is a ento-thyroidal system in pregnancy HCT elevates oid function and TBG increased by estrogen carries oid hormone to target organ

s established that the thyroid gland becomes rged and hyperplastic (1 2) thyroidal uptake of oiodine is increased (3 4) and the serum ein bound iodine (PBI) is elevated during preg cy (5 6) This may be interpreted as being due thyroid stimulating substance that exists in the ian placenta suggested by Akasu et al (1955) (7) Later a purified protein with TSH activity was extracted by Hennen et al (1969) (8) Hershman et al (1971) (9) and a highly purified glycoprotein with TSH activity was extracted from the human term placenta by the authors (1972) (10) This prote in hormone is called human chorionic thyrotrophin (HCT) or human chorionic thyroid stimulating hormone (HCTSH) The authors reported the bio- logical biochemical immunological character of this hormone (11) and the serum HCT level was estimated by radio-immunoassay using 131 IHCT and anti HCT serum (12) In this paper the pla cento-thyroidal relationship during pregnancy is discussed

MATERIALS AND METHODS

Clinical materials

Estimations of HCT TSH T3 T4 PBI ETR Triosorb TBG binding capacity BMR and estrogen were made si multaneously in 160 women in normal pregnancy at the Reproduction Clinic Kobe University Hospital TRH stimulation tests were made in ?0 ca es of each trimester of pregnancy The women tested had no previous history of thyroid disease and none were on medication

Laboratory methods

Serum HCT was measured by radioimmunoassay as de scribed in a previous paper (12)

Serum HTSH and serum T3 were determined by radio- immunoassay using kits of Daiich Radioisotope Laborato- ries Serum T4 and effective thyroxine ratio (ETR) were measured with Res O Mat T4 Kit and Res-O-Mat ETR Kit of Mallinckrodt Corporation Serum protein bound iodine (PBI) was measured by the auto-analyzer technique and basal metabolic rate (BMP) was determined with the Sanborn-type Metabulater Tri-iodo-thyronine resin sponge uptake (T3-RSU) was measured with a Triosorb Kit The binding capacity of TBG was determined accord ing to the method of Ingbar et al (13) The total estrogen

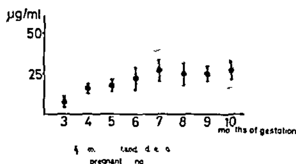


Fig 1 HCT during normal pregnancy

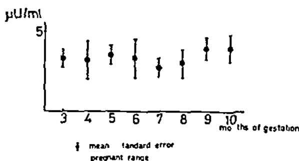


Fig 2 HTSH during normal pregnancy

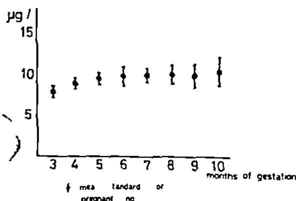


Fig 3 T_4 during normal pregnancy

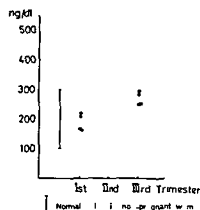


Fig 4 T_3 during normal pregnancy

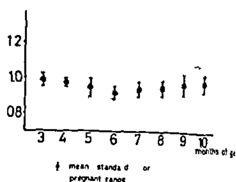


Fig 5 ETR during normal pregnancy

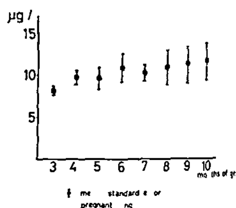


Fig 6 PBI during normal pregnancy

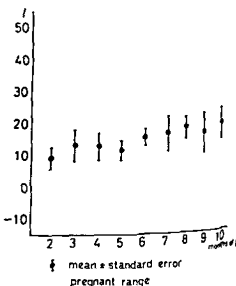
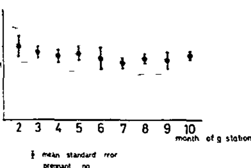
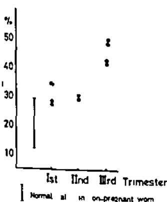


Fig 7 BMR during normal pregnancy



8 Triosorb during normal pregnancy



9 TBG binding capacity during normal pregnancy

ine was determined according to the method of Brown with some modifications The TRH stimulation tests performed as following 100 µg of TRH synthesized ie Daigo Nutritive Chemicals Ltd was given intrave ly as a rapid injection Serum TSH and serum HCT determined before and ?0 30 45 60 90 and 120 min injection

RESULTS

T was detectable even in early pregnancy It eased progressively during pregnancy and hed a level of 12 5–50 0 µg/ml at term (Fig 1) I level remained within the non pregnant range letectable–10 µU/ml) throughout the course of mancy (Fig 2) T4 gave a value of 7 5–12 0 o in early pregnancy 7 5–15 0 µg% in middle mancy and 8 0–16 5 µg% in late pregnancy ing to increase within the non pregnant range 14 0 µg%) toward the end of pregnancy 3) T3 gave a value of 150–250 ng/dl in the ?10–320 ng/dl in the second and 210–310 ng/dl e third trimester of pregnancy tending to in se progressively within the non pregnant range

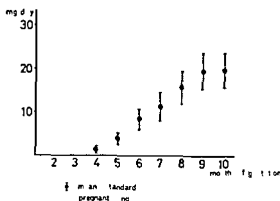


Fig 10 Urinary total estrogen during normal pregnancy

(100–300 ng/dl) (Fig 4) ETR remained within the range for non pregnant status (0 8701 13) through out the course of pregnancy (Fig 5) PBI increased progressively (non pregnant range 4 7–8 0 µg/dl) (Fig 6) and BMR showed a slight increase (non pregnant range −5–+15%) (Fig 7) Triosorb gave a value of 20–30% in early pregnancy and de creased progressively during pregnancy (non preg nant range 26–36%) (Fig 8) TBG binding capacity gave a value of 26–36 µg% in the first 28–55 µg% in the second and 36–51 µg% in the third trimester

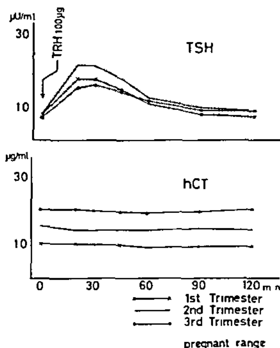


Fig 11 TRH test in normal pregnancy

of pregnancy (Fig 9) and to be accompanied by a rise in urinary estrogen (Fig 10)

The effect of TRH on the TSH level and HCT level was studied in each trimester of pregnancy (Fig 11) A peak of TSH occurred at 20–30 min after the TRH injection with a gradual fall over the next 120 min in all cases and the level of the TSH peak was similar to that of non pregnant women TRH did not influence the HCT level in any pregnant subject

DISCUSSION

This paper demonstrated that the concentration of thyroid hormone increased progressively during pregnancy and it was previously reported by the authors that serum thyrotrophic bioactivity was elevated obviously and increased progressively during pregnancy

Malkasian et al (15) and Souma et al (16) guessed that using estrogen levels caused an increase in thyroid function They made this assumption from two well known facts 1) The thyroid function of pregnant women is similar to that of patients receiving birth control pills or estrogen 2) The thyroid function of the women on the pill is significantly elevated In other words it may be due to an over response of the thyroid caused by the elevation of TSH because of over thyroxine binding of TBG However the serum TSH level in pregnant women measured by radio immunoassay is neither elevated as high as is expected from its bioactivity nor increased progressively It remained essentially the same throughout the course of pregnancy as in the non pregnant state Moreover it was suggested by the TRH stimulation test that the pituitary TSH secreting function of pregnant women was similar to that of non pregnant women For that reason TSH does not seem to increase thyroid function in pregnancy There must be some other explanation for the high thyrotrophic bioactivity in the serum of pregnant women and the increasing blood concentration of thyroid hormone

It was previously suggested by Akasu et al (1955) that the human placenta might have a TSH like activity Recently the authors succeeded in extracting a highly purified glycoprotein (HCT) from the human term placenta which has a highly specific TSH activity and they have demonstrated that immunologically it has no cross reactivity with human pituitary TSH and it is different from other placental protein hormones such as [illegible] and HCS

The authors planned to measure serum HCT by radio-immunoassay using 131 I HCT and HCT In this radio-immunoassay developed by [illegible] authors HCT gave a value of 3 0–25 0 μg/ml [illegible] first 10 0–40 0 μg/ml in the second and 1[illegible] μg/ml in the third trimester of pregnancy [illegible] creased gradually toward the end [illegible] like thyroid hormone These findings sugges[illegible] hyperfunction of the thyroid during preg[illegible] may not be due to high estrogen high T[illegible] free thyroxine negative feed back high TSH [illegible] tion but to HCT originating from the placenta

In spite of the thyroid hormone increase it [illegible] that the clinical picture of hyperthyroidism [illegible] manifest among pregnant women and ET[illegible] mained within the non pregnant range throu[illegible] the course of pregnancy and Triosorb decr[illegible] progressively during pregnancy This may be i[illegible] preted as being due to the increase of TBG b[illegible] capacity which is increased progressively and b[illegible] more of the free thyroxine during pregnancy [illegible] a change in TBG binding capacity is well know[illegible] be caused by the effect of estrogen which is re[illegible] ably increased during pregnancy (17)

From these results the authors introduce the [illegible] cept of a placento-thyroidal system in pregnan[illegible] summary in non pregnant women thyroid func[illegible] is controlled by pituitary TSH (pituitary-th[illegible] system) In pregnant women it is possible [illegible] thyroid function is controlled slightly by pi[illegible] TSH but is never elevated by pituitary T[illegible] Thyroid function in pregnant women is eleva[illegible] HCT itself which has a higher activity in [illegible] than that of TSH Meanwhile TBG binding ca[illegible] ity increased by estrogen binds more th[illegible] hormone and keeps free thyroxine in the [illegible] pregnant range TBG neither elevated the s[illegible] TSH level nor altered thyroid function pro[illegible] sively toward the end of pregnancy

As mentioned above it is possible to say th[illegible] thyroid gland and thyroid hormone secretion [illegible] controlled by HCT and estrogen originating [illegible] the placenta (placento-thyroidal system)

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SERUM ALKALINE PHOSPHATASE IN PREGNANCY

II Serial $HSAP_{65°C}$ Estimations in Pregnancy Complicated with Hypertension and Pre eclampsia

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ict This is a study of heat stable alkaline hatase ($HSAP_{65°C}$) concentrations in the serum of int women with hypertension (42 cases) mild pre psia (40 cases) and severe pre-eclampsia (72 cases) sults are seen in relationship to the occurrence of terine fetal death growth retardation intrauterine eonatal asphyxia as well as the respiratory distress ome (RDS) in the newborn The importance of a e clinical classification of the patients is stressed logical HSAP values are those which lie either over ler the normal range for HSAP activity In addition zag curves with values within the normal range are terized as abnormal Thus serial estimations give ost reliable results Serial estimations of HSAP are ially valuable in severe pre-eclampsia Abnormal values in the 28th–38th week of pregnancy are a s prognostic sign False abnormal HSAP results found in all 3 patient groups One possible false d HSAP curve also occurred

placenta is an organ of high metabolic activity h contains large amounts of different enzymes P is one of the enzymes of most interest—part ecause its chemico physical characteristics it easier to measure and separate from other nzymes of alkaline phosphatase—and partly use the occurrence of placental alkaline phatase (HSAP) in maternal serum can possi e used as an indicator of placental function (1 7 10)

ough the enzyme has been known since the le of the 1930 s it is only in the last 10 years determination of HSAP in maternal serum has used as placental function test (1 2 5) Some ors have assessed that in high risk pregnancies ctivity of HSAP in maternal serum is a good meter of placental function while others have denied this correlation (2 3 4 5 6 7) This dis agreement can partly be explained by experimental discrepancies—for example variation in tempera ture at inactivation time buffer etc (2 3 5 7 10) In some studies the activity of HSAP in maternal serum is correlated with fetal weight in some with placental weight and in some with both fetal weight and fetal distress (2 3 5 7 10)

In an earlier study we determined total alkaline phosphatase (TAP) in the serum from healthy preg nant women from the 18th week of pregnancy until term Simultaneously we did a fractionated de termination of $HSAP_{60°C}$ and $HSAP_{65°C}$ as well as L phenylalanine sensitive alkaline phosphatase We found that it was only with inactivation at 65°C that the enzyme activity in maternal serum rose con stantly from the 24th–25th week until term (9)

In this study we have evaluated the results of serial determination of $HSAP_{65°C}$ in the serum of pregnant women with hypertension and pre eclampsia We have used serial determinations because zig zag curves are pathological even though individual values lie within the normal range (5 6 9 10) The HSAP curve for each patient has been related to the baby s condition at birth as sessed by a number of clinical criteria which are re lated to placental function during pregnancy and/or during delivery

MATERIAL AND METHODS

The series consists of 104 pregnant women admitted to the unit suffering from hypertension or pre-eclampsia The classification is given in Table I The blood pressure read ing which was used for allocation of the patient to one of

Table I

Diagnosis	Features	No of patients
1 Hypertension	BP >140/90 Normal urine No oedema	42
2 Mild pre eclampsia	BP >140/90 to 160/110 Proteinuria 0 5–2‰ Oedema	40
3 Severe pre eclampsia	BP≥160/110 Proteinuria ≥2 Oedema	22

Table II *Serial HSAP determinations in serum from patients with hypertension and pre eclampsia*

Group of patients	Normal HSAP curves	Abnormal HSAP curves	Total
Hypertension	10	32	42
Mild pre-eclampsia	7	33	40
Severe pre eclampsia	0	22	22

Table III *Hypertensive and pre eclamptic women with normal HSAP curves Fetal status*

Groups of patients	Perinatal asphyxia RDS stillbirths	Weight ≤ 2 per centile	Weight > 2 per centile	Total
Hypertension	0	1	9	10
Mild pre eclampsia	0	0	7	7
Severe pre eclampsia	0	0	0	0

the three groups was taken after at least two hours bed rest on the day of admission Indication for delivery—the time and the method—was decided on the basis of the case history clinical findings and other placental function tests such as oestriol estimations The development and maturity of the fetus was assessed on the basis of serial ultra sound measurements and determination of surfactant in the amniotic fluid The results of HSAP determinations were *not included in the assessment of* indication for delivery Caesarean section was performed on fifteen women because of serious placental insufficiency In the remaining cases contractions either started spontaneously or were induced by oxytocin before or after the expected date of delivery Intrauterine asphyxia or prolonged second stage of labour resulted in 16 forceps deliveries and 2 vacuum extractions Two of the vaginal deliveries were breech presentations All the operative deliveries resulted in live births If the was under 37 weeks the baby was classif Of the premature babies there were 3 in gro p I sion) 3 in group II (mild pre-eclampsia) and 4 in group III (*severe pre-eclampsia*) Intrauterine asphy diagnosed clinically or by cardio-tocography The nation neonatal asphyxia was applied to those Apgar score of 6 or less one or five minutes The weight of the baby was related to a percentile worked out on the basis of the weight of all babies in Norway during the period 1967 1968 (for Social Medicine and Public Health Univer Bergen Norway)

HSAP was estimated 1–2 times weekly betw date of admission and delivery Groups I and II were usually admitted so near term that tests were for only 2–3 weeks Group III patients were all for several weeks and serial estimations were obtained over a longer period from these patie results are assessed on the basis of changes during pregnancy Two types of pathological cu described

1 Curves where one or more H the normal range

2 Curves with varying individual values wh within the normal range (zig zag curves)

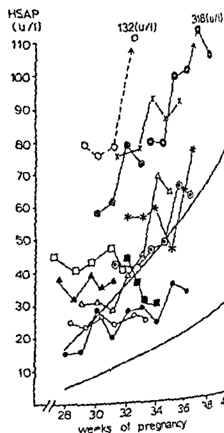


Fig 1 Serum HSAP curves from hypertensive eclamptic mothers with fetal death in utero

e IV *Hypertensive and pre eclamptic women with abnormal HSAP curves Fetal weight distribution*

ps of patients	Weight ≤ 2 percentile	Weight= 3–5 percentile	Weight= 6–9 percentile	Weight ≥ 10 percentile	Total
rtension	8	7	3	14	3
pre-eclampsia	5	8	3	17	33
e pre-eclampsia	14	[illegible]	2	4	2[illegible]

RESULTS

patients with severe pre-eclampsia (group III) pathological HSAP curves some with one or abnormally low values some with abnormally values and some with zig zag values within normal range On the other hand the patients hypertension (group I) and mild pre-eclampsia p II) had respectively 76 2% and 82 5% rmal HSAP curves (Table II) Seventeen of the patients had normal HSAP curves Of these 17 were 10 in group I and 7 in group II One of patients in group I gave birth to a child with ficant growth retardation (<2 percentile) but all others delivered healthy babies with weight >2 entile (Table III)

thological HSAP curves showed a close corre n with growth retardation in all 3 groups this lation being most pronounced in group II (Ta V)

ther risk factors occurred frequently in connec with pathological HSAP curves In all cases of uterine death the HSAP values were abnormal in the 3rd trimester (Fig 1) In all cases of natal asphyxia and RDS the HSAP curves were abnormal (Table V)

DISCUSSION

ental function tests are of value in predicting l status Placental insufficiency can result in r nutritional function with possible retardation in fetal growth The respiratory function of the placenta can also be reduced resulting in in trauterine death perinatal asphyxia or RDS during the first day of life In our evaluation of the HSAP results we have taken into account all these abnor mal states of the fetus and the newborn

We do not attempt to assess the prognostic value of HSAP in relation to other placental function tests Our aim here has been to examine to what extent serial estimations of HSAP in maternal serum mirror the function of the placenta what limits the methods has and what practical conse quences the results may have

In severe pre-eclampsia there is often marked destruction of placental tissue while in transient hypertension and pre-eclampsia there is seldom such a degree of placental damage that the fetus is affected This is reflected in our results (Table II) Mild hypertension or pre eclampsia together with a normal HSAP curve seems to be associated with less risk to the fetus than the corresponding hypertension and pre-eclampsia combined with pathological HSAP curves (Tables III and IV) However there was one baby with fetal growth retardation in the normal HSAP group (Table III) The baby survived and at 17 months of age it was of normal weight and development There are many possible explanations for this one being a false normal HSAP

Where the HSAP curves were abnormal there was a marked tendency to growth retardation in all

le V *Hypertensive and pre-eclamptic women with abnormal HSAP curves Fetal status*
ber in parentheses gives simultaneous growth retardation

ps of patients	Fetal death	Perinatal asphyxia RDS	Healthy children weight ≤ 2 percentile	Healthy children weight > 2 percentile	Total
ertension	2 (2)	14 (3)	3	13	32
pre-eclampsia	1 (1)	11 ([illegible])	2	19	33
re pre-eclampsia	9 (9)	7 (3)	2	4	22

3 groups (Table IV) most pronounced in severe pre eclampsia There were also more intrauterine deaths perinatal asphyxia and RDS Interpretation of the results is to some extent difficult since there were 10 live born premature babies and prematurity itself predisposes to RDS In all cases of intrauterine death and several of perinatal asphyxia there was also growth retardation (Table V) Thus disasters to the fetus and the newborn may well occur in connection with pathological HSAP curves particularly in the presence of severe pre eclampsia

In the 3 clinical patient groups there were 36 healthy babies with weight over 2 percentile even when the HSAP curves were abnormal (Table V) Other workers have demonstrated the same tendency (3) However it is worthwhile to recognize that about 60% of the newborn babies from mothers with abnormal HSAP curves had a weight less than the 10th percentile (Table IV)

Pathological HSAP concentrations in maternal serum probably imply degeneration of placental tissue This can occur during a short period with moderate symptoms without straining the reserve capacity of the placenta

From the findings it seems that the prognosis for the fetus is relatively good if there is no growth retardation (Table V) Pathological HSAP curves in maternal serum do not seem to indicate the danger of fetal death in the following days (Fig 1) But severe pre-eclampsia combined with abnormal HSAP curves means that the fetus is in considerable jeopardy Pathological HSAP curves early in 3rd trimester are a serious prognostic sign This is in agreement with other studies (1 6) The deciding factors are the severity and duration of the disease From Fig 1 it will be clear that if only a single determination of HSAP is carried out in each case it might probably be recognized as normal However from the study of serial determinations and clinical outcome it is clear that this would have been a wrong conclusion

It is unlikely that a single placental function test can reflect all the metabolic processes of the placenta Serial HSAP estimations have limitations but seem to be of value If pathological HSAP curves occur in connection with pre eclampsia termination of the pregnancy should be conside[illegible] decision however should be taken on[illegible] studying the total clinical and laboratory p[illegible]

The estimation of HSAP is particularly [illegible] while as a supplement to other placental f[illegible] tests and ultra sound techniques HSAP is quick cheap and simple to carry out

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STUDIES IN DIABETIC PREGNANCY

I Serum Lipids

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ict The serum lipid values at different stages of n twenty six pregnant diabetic women attend antenatal clinic at the Department of Obs and Gynecology were compared with the corre ing values in four control series composed of pregnant women Control series were studied ks 10 22 34 and after delivery respectively Serum erides were higher in the diabetic women at week 10) week 34 ($p<0\ 05$) and after delivery ($p<0\ 05$) rmore in the diabetic women infant birth ts were correlated ($r=0\ 52$ $p=0\ 05$) with maternal triglyceride values at week 31 Women with the t serum triglyceride values (>250 mg/100 ml) were red of infants with a higher birth weight ($p<0\ 05$) hose women with lower serum triglyceride values mg/100 ml) Intra uterine deaths ($n=4$) were not re to maternal serum triglyceride values but mean glucose values (during the whole pregnancy) were ($p<0\ 001$) in mothers with intra uterine deaths ted plasma free fatty acids (FFA) in the diabetic r would be a possible cause for elevated serum erides through increased liver triglyceride synthe hile in the fetus an excess of plasma FFA (passing gh the placental barrier) together with normal or ele plasma insulin would be a likely explanation for ased triglyceride synthesis in adipose tissue and by of increased fat depots and body weight

formal pregnancy maternal serum cholesterol triglyceride values show a characteristic and essive increase toward the third trimester (4 9 In diabetic pregnancy only limited informa is available as to serum lipid and lipopro- changes

abetic pregnancy however has long been vn to be linked with high infant birth weight and termore this over weight of the infant has shown to be due to an excess of fat acquired ng intra uterine life The lack of correlation be n maternal blood glucose values and infant birth weight (7) directs interest toward other metabolic variables in diabetic pregnancy

The aim of the present study was to compare serum cholesterol and triglycerides in diabetic preg nancy with the values found in normal pregnant women Furthermore attempts were made to relate serum lipid variables and blood glucose to pediatric data and to the fetal outcome

MATERIALS AND METHODS

Clinical series Twenty six consecutive pregnant women with diabetes mellitus age 19–36 years (mean 26 3) were studied at six occasions during and after pregnancy week 10' (range 7-13) week 19 (range 18–20) week 25 (range 24– 6) week 31 (range 30-32) week 37 (range 36–38) and once after delivery at day 2–5

The women of the diabetic series attended at regular intervals a special antenatal clinic at the department of Obstetrics and Gynecology Each woman was admitted to hospital at least once during the first and the second trimester and was kept in hospital from approximately week 30–32 until term Each woman with diabetes re quired insulin treatment before pregnancy All diabetic women were otherwise in good health and their diabetes was well-controlled The women were grouped in relation to the degree of severity of the diabetes according to White (16) as follows Eight women were judged as class B eight in C nine in D and one woman in cla s F

Four different groups of women with normal pregnancy without any history or symptoms of metabolic disease served as a *control series* in the comparison of serum lipid data The four groups of women were studied at week 10' (range 8-12) ($n=20$) week 22 (range 0–24) ($n=20$) week 34 (range 30–37) ($n=20$) and after delivery day 2–5 ($n=10$) In the comparison of serum lipid values data during diabetic pregnancy in week 19 and week 25 were combined designated as week 22" and data obtained during week 31 and week 37 as week 34

The answers obtained at term by a questionnaire given to 112 consecutive women with normal pregnancy were

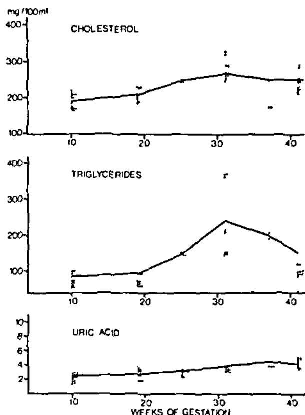


Fig 1 Diabetic pregnancy Serum cholesterol triglycerides and uric acid at various stages of pregnancy and after delivery Number of subjects week 10 $n=20$ week 19 $n=16$ week 25 $n=14$ week 31 $n=21$ week 37 $n=8$ and post partum $n=20$ Mean ±SEM

used in the comparison of obstetric data (*control series*)

Blood sampling Blood samples were drawn from an anti-cubital vein in the fasting state in the morning after the clinical examination After clotting the blood was centrifuged at 2500×g for ten minutes and serum was recovered

Serum lipids and uric acid Cholesterol and triglycerides were determined by standard automated procedures and uric acid (normal for females <6 2 mg/100 ml) according to standard methods in the Clinical Chemistry Laboratory

Statistical methods Conventional methods were used for the calculation of means standard deviations and standard error of means Student s *t* test was used to evaluate differences between groups and qualitative data were compared by chi square test Values of $p \leq 0\ 05$ were considered to be statistically significant (1)

RESULTS

Clinical data The present series of pregnant diabetic women was characterized by a higher ($p<0\ 01$) incidence (50%) of diabetes mellitus among their relatives than women in the control series (?) Also in agreement with earlier experience in diabetic women (2 6) these pregnant diabetic women reported a high frequency of vaginitis ($p<0\ 01$) as well as of urinary infections ($p<0\ 05$) There was no difference in the diabetic and control series regarding the onset of menstruation duration of menstrual bleeding or the intervals between periods There was a tendency to a higher incidence of spontaneous abortions in the diabetic series (?) than in the control series (?0%) Fertility however was identical in the two series

Serum lipids Serum cholesterol and in particular serum triglycerides increased successively during pregnancy both in series of diabetic women and control series Both serum lipids showed a maximum level in third trimester In the diabetic series at week 31 serum cholesterol had increased (compared to week 10) by 37% and serum triglycerides by 185% (Fig 1)

After delivery within 2–5 days serum lipids declined in both series (Fig 2) Serum cholesterol as well as triglycerides were however still higher (compared to week 10) in diabetic series $p<$? and $p<0\ 001$ respectively and in control series $p<0\ 001$ and $p<0\ 001$ respectively

Serum lipids in diabetic pregnancy as compared to the values in control series (Fig 2) There were no differences in mean *serum cholesterol* levels between the diabetic and control series at weeks 22 34 or after delivery Pregnant women with diabetes had however higher mean *serum triglycerides*

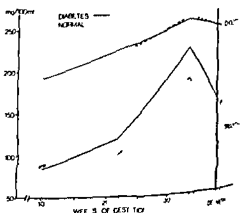


Fig 2 Diabetic ($n=26$) and normal (n ?0) pregnancy Mean values of serum cholesterol and triglycerides at various stages of pregnancy after delivery
$p<0\ 01$

05 p<005

2000 2500 3000 3500 4000 g
INFANT BIRTH WEIGHT

1 Diabetic pregnancy Relationship between mater um triglycerides (at gestational week 31) and infant weight $y=0.09x-60.6$ $r=0.52$ $p<0.05$ $n=18$

alues at week 10 ($p<0.01$) at week 34 ($p<$ and after delivery ($p<0.05$)

ernal serum lipids in relation to infant birth (Fig 3) In the diabetic series ($n=18$) there positive correlation ($r=0.52$ $p<0.05$) be serum triglycerides of the mother (in week d the birth weight of the infant In the control 34 series ($n=20$) no such correlation be maternal serum triglycerides and infant birth was found

he diabetic series when *women were divided* ation to their serum triglyceride values at 31 those ($n=9$) with serum triglycerides >250 0 ml were subsequently delivered of infants higher ($p<0.05$) mean birth weight than wo $n=1?$) with serum triglycerides <250 mg/100 able I) In these two groups of pregnant wo vith diabetes there was no difference between blood glucose values as determined through egnancy (124±13 and 98±4 mg/100 ml re vely) These two groups did not differ in mat a e (?8±3 and 24±1 years respectively) in ional age in the length of the infants or the t of the placentas (Table I)

he diabetic series no correlation was found en maternal mean blood glucose values ghout pregnancy) and infant birth weight

a-uterine deaths in relation to serum lipids d glucose In the diabetic series ($n=26$) ntra uterine deaths occurred and one mother spontaneous abortion in the 3rd month The diabetic mothers with intra uterine deaths had r ($p<0.001$) mean blood glucose values ghout pregnancy) than *twenty-one mothers* red of live born infants (Table II) In these ries ($n=4$ and $n=21$ respectively) there were ferences in maternal mean triglyceride values ek 10 or in week 31

The four mothers with intra uterine deaths were delivered at an earlier gestational age (three infants in week 35 and one infant in week 33) than those twenty-one with infants born alive (mean gesta tional age 37 8 weeks)

DISCUSSION

The present series of pregnant diabetic women was characterized by a high (50%) familial incidence of diabetes mellitus and frequently a history of vag initis (57%) and of urinary infections (46%) and also a tendency to spontaneous abortions On the other hand the finding of normal regular menstrual periods as well as of fertility comparable to the control series was evidence that the present series of pregnant diabetic women should be considered as a representative and well-controlled group of diabetic women

During pregnancy the diabetic women like wo men with normal pregnancy showed a successive increase in serum lipids preferentially in serum triglycerides with a maximum level in the third *trimester The diabetic women however revealed* even higher serum triglyceride values at week 10 ($p<0.01$) and at week 34 ($p<0.05$) than women in the control series The finding in diabetic pregnancy of a marked serum triglyceride elevation in the third trimester was recently reported by Knopp et al (8) In diabetic pregnancy also a marked increase in pre β lipoproteins (*the major triglyceride trans* porting lipoprotein) has been revealed by serum lipoprotein electrophoresis (11 15) Earlier data (5 8) would indicate however that at least in normal pregnancy an increase in serum triglycerides would only partially be due to an increase in pre β-lipoproteins (VLDL) but also be explained by a *higher content of triglycerides in high density* lipoproteins (HDL) Studies now in progress in

Table I *Maternal serum triglyceride values (TG) in week 31 compared with pediatric data*
Mean ±S E M

	n	Delivery week	*Infant* weight (g)	*Infant* length (cm)	*Placental* weight (g)
TG>250	9	37±0 7	3781±65	50±1 4	716±53
TG<250	1	38±0 4	3108±164	49±0 8	601±32
$p<$		NS	0 05	NS	NS

Table II *Maternal blood glucose and serum triglyceride values compared with pregnancy ou*tco
Mean±S E M

	n	Blood glucose whole pregnancy (mg/100 ml)	Triglycerides whole pregnancy (mg/100 ml)	Triglycerides week 31 (mg/100 ml)
Live births	21	100±17	155±11	234±24
Intra uterine deaths	4	160±15	143±33	269±64
$p<$		0 001	N S	N S

normal and in diabetic pregnancy would hopefully throw further light on this question of great importance in the understanding of serum lipoprotein derangements in pregnancy

In diabetic pregnancy the birth weight of the infant appears to be related ($r=0\ 52$ $p<0\ 05$) to elevated maternal serum triglyceride values (when triglycerides are determined in third trimester) In normal pregnancy however no correlation was found between infant birth weight and maternal serum triglycerides Elevated pre β lipoproteins (15) but not serum triglycerides have earlier been linked to intra uterine deaths in diabetic pregnancy In the present study however there was no relationship between maternal serum lipid values and intra uterine deaths but mean blood glucose values were higher ($p<0\ 001$) in diabetic women who experienced intra uterine deaths

In earlier studies (7) the lack of correlation between infant birth weight and maternal blood glucose values has directed the interest in this respect towards other metabolic variables in diabetic pregnancy (14) In diabetic pregnancy the serum lipid changes are also characterized by a high level of free fatty acids (FFA) (10) and recently a relationship between FFA and infant birth weight has been shown (10) Elevated serum triglycerides found in the present study as a possible indicator for infant overweight would however for practical purpose be an easier variable than FFA to measure and evaluate

Increased serum triglycerides can either be due to an increased formation or a decreased removal (catabolism) Lipoprotein triglyceride synthesis occurs preferentially in the liver Certain metabolic factors such as blood glucose plasma insulin and FFA appear to influence triglyceride synthesis An excess of FFA would enhance liver triglyceride synthesis (12) and when present simultaneously with elevated plasma insulin and blood glu[cose] stimulate triglyceride synthesis in the adipose [tissue] (3) In diabetic pregnant women elevated F[FA] might be a cause for increased serum trigl[ycerides] Furthermore in the light of recent [..] knowledge on placental transfer of FFA ([..] creased FFA in the diabetic pregnant wo[man] would be expected to cause elevated FFA [in the] fetus Increased FFA simultaneously with [..] or even elevated plasma insulin and access [..] cose would in the fetus be a likely cause fo[r in]creased triglyceride synthesis in adipose ti[ssue] These series of events might be one possib[le ex]planation for a relationship between maternal se[rum] triglyceride values and increased infant birth w[eight] in diabetic pregnancy

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INHIBITORY EFFECT OF DECIDUA ON FIBRINOLYSIS INDUCED BY UROKINASE AND BY THE FIBRINOLYTIC ACTIVITY OF THE RAT OVUM

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ract With the use of a technique which permits the y of fibrinolytic enzymes and inhibitors in organ ure human decidua was found to produce inhibitors ible of inhibiting plasminogen activation induced by nase as well as activators released from kidney ex ts Also the medium in which rat and human decidua been cultured was found to inhibit fibrinolytic activity he rat ovum The inhibitors emanating from the de ia are presumably of importance for facilitating the lantation of ova

formation of decidua is accompanied by a de ase in the fibrinolytic activity of the en netrium (1 2) This decrease is believed to be an ortant factor in supporting nidation The low nolytic activity of the decidua as determined tochemically might depend upon a low plas iogen activator content and/or a high content nhibitors of fibrinolysis

Recently a method has been devised for the study fibrinolytic activators released in organ culture In this method explants are cultured in the sence of but not in contact with a preformed ndard fibrin clot Fibrinolytic activators released the medium during culture cause the gradual akdown of the clot Determination of the stable rin degradation products (FDP) accumulating in medium provides an indirect measure of the iount of fibrinolytic activators released The thod has also been found to be suitable for the dy of inhibitors released (4) Using this method studied the inhibitory effect of human decidua the action of urokinase and of fibrinolytic ivators released by human kidney explants We o studied the influence of inhibitors produced in organ culture by human and rat decidua on the fibrinolytic activity of the rat ovum

MATERIAL AND METHODS

Kidneys were taken from 16 to 18 week old fetuses obtained at legal abortion operations performed for sociomedical reasons on physically healthy women The fetuses were removed by hysterectomy The decidua was taken at the same time from a site opposite to the placenta in the uterus

The tissue fragments were washed in Parker 199 (SBL Stockholm) culture medium and divided into pieces about 1 mm across These explants were then placed on slices of gel foam (Spongostan Ferrosan Malmo) four explants per slice The slices of gel foam with the explants were transferred to Leighton tubes (two slices in each tube) containing a clot formed by addition of 0 04 ml of thrombin (Topostasin Roche) diluted to 75 NIH U/ml in Parker 199 to 1 ml of a solution of one gram of fibrinogen 80 ml of distilled water and 0 ml of Parker 199 One millilitre of the culture medium Parker 199 was then added Care was taken to avoid contact between the sponge slices and the preformed clot In the experiments performed to assess the inhibitory effect of decidua on urokinase decidua explants were cultured in medium containing respectively 3 0 1 5 0 75 Ploug units of urokinase/ml (Lovens Copenhagen) Each Leighton tube contained two slices of gel foam with four decidua explants on each For comparison the same test system was incubated with the same amounts of urokinase but without decidua explants

In the combined cultures two explants of decidua and two explants of kidney were placed on each slice of gel foam Gel foam slices without explants placed in similarly prepared Leighton tubes served as controls

After culture the kidney explants were examined for fibrinolytic activity with Todd s fibrin slide method (5) as modified by Pandolfi (6)

For determination of FDP 0 06 ml of culture medium

Table I *Inhibition of urokinase by decidua in organ culture Values given for two cultures Each value denotes FDP (mg/ml of Parker medium)*

	Days of culture					
	I		II		III	
Urokinase 3 0 U/ml	150	156	216	240	448	500
+Decidua	12	18	62	76	110	130
Urokinase 1 5 U/ml	25	30	75	100	180	210
+Decidua	7	7	19	25	32	45
Urokinase 0 75 U/ml	1 5	2	13	17	50	70
+Decidua	0	0	0	1	4	6
Decidua	0	0	0	0	1 5	2
Control	0	0	0	0	0	1

was collected every 24 hours with a capillary pipette FDP were determined with a quantitative immunological method (7)

An experiment was performed in which human decidua as well as rat decidua was first cultured as organ culture for three days in Parker medium without a preformed clot Both culture media were then examined for their ability to inhibit fibrinolytic activity of the rat ova in the following way glass slides were prepared covered with a fibrin film This film was obtained by mixing 0 06 ml of fibrinogen (bovine fibrinogen prepared essentially according to Brakman s modification (8) of Astrup and Müllertz s (9) double ammonium sulphate precipitation method in a concentration of 1% in phosphate buffer pH 7 8 ionic strength 0 15) and of 10 µl thrombin (Topostasin 20 NIH U/ml unbuffered saline) The fibrinogen thrombin mixture s spread over an area of 10 cm² in order to obtain a film about 0 07 mm thick To stabilize the fibrin film slides were left at room temperature (21–24 C) in a st chamber for 30 minutes

To some of the slides decidua culture medium and to some serving as controls Parker medium 199 not previously used for culture was added to the thrombinfibrinogen mixture to a final concentration of 40% Rat ova obtained by flushing the fallopian tubes on day 2 of pregnancy and washed in physiological saline were transferred to the fibrin film with a micropipette The slides were then incubated in a thermostatically controlled (23 C) moist chamber for 30 minutes The lytic area in the fibrin film was then calculated in square microns of lysis Fifteen ova were examined on each kind of slide prepared

RESULTS

The inhibitory effect of decidua explants on the activation of plasminogen by urokinase is apparent from Table I which shows a marked inhibition in all the concentrations used In the concentration of 0 75 Ploug units per ml of medium the inhibition was almost complete There was a co[illegible] release of fibrinolytic enzyme from the renal [illegible] plants as measured by the increase in FDP [illegible] culture medium When the renal explants [illegible] cultured together with decidua explants the [illegible] of FDP was much smaller (Table II)

In the controls and the cultures of decidua [illegible] FDP were barely detectable on the third day

The fibrinolytic activity of the rat ova [illegible] on fibrin slides without culture medium or [illegible] addition of fresh medium was found to [illegible] $90 \pm 10 [\times 10^3]$ square microns On the slides [illegible] which human decidua culture medium or that of decidua was added to the fibrin film the area [illegible] fibrinolytic activity never exceeded the area of the ovum i e $< 18 \times 10^3$ square microns

An additional experiment was performed [illegible] which decidua and human fetal lung tissue [illegible] first cultured as organ cultures for two days [illegible] Parker medium without a preformed clot [illegible] medium from these cultures was then used [illegible] medium for kidney cultures in Leighton tubes [illegible] a preformed clot and also examined for its ability [illegible] inhibit urokinase We found that the medium [illegible] decidua cultures but not from lung cultures [illegible] bited activation of plasminogen by urokinase and the enzymes liberated from the kidney explants Histochemical examination of the cultured [illegible] explants invariably revealed persistent fibrinolytic activity

DISCUSSION

The results show that human decidua in organ culture liberates agents capable of inhibiting the activation of plasminogen by urokinase as well as the fibrinolytic activators released by kidney explants That the inhibitory effect of the decidua [illegible]

Table II *Inhibitory effect of decidua on a[illegible] fibrinolytic activity in kidney organ cultures*

Values given for two cultures Each value denotes F[illegible] (mg/ml of Parker medium)

	Days of culture					
	I		II		III	
Kidney	8	32	125	168	400	[illegible]
Kidney+Decidua	0	3	4	9	9	[illegible]
Decidua	0	0	0	0	0.5	[illegible]
Control	0	0	0	0	0	[illegible]

be ascribed to adsorption of the activators to the ace of the decidua explants is apparent from the itional experiment in which the medium from decidua culture had an inhibitory effect while from lung tissue had not The persisting inolytic activity found in the kidney explants ins that the inhibitory action takes place in the lium

he results also demonstrate that the inhibitors ased by human as well as by rat decidua ex its in organ culture are capable of inhibiting the inolytic activity of the rat ova It has been wn recently that rat ova possess a high fibrino- activity during their passage through the fallo- 1 tube This activity decreases when the ova hes the uterus and disappears at implantation During the formation of decidua the fibrino- activity of the endometrium decreases (1 2) It been assumed that the decrease in the fibrinoly activity of the endometrium and the disappear e of the fibrinolytic activity of the ovum is of ortance for implantation This is analogous to situation in organ culture on clotted substrates en fibrinolytic active explants are placed on clot substrates they dissolve the substrate and be ie detached (11 12 13) The addition of an bitor of fibrinolysis prevents this and promotes resion and growth (13 14 15) Judging from the sent observations inhibitors derived from the idua are capable of inhibiting not only inolysis induced by urokinase but also the inolytic activity of the rat ovum This suggests t the decidua inhibitors are of importance for litating implantation of the ovum

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A PROSPECTIVE STUDY OF DRUGS AND PREGNANCY

3 *Hormones*

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ract Results from a prospective study in Malmö ormed in 1963–65 are used to discuss the possible role ormonal drugs in human fetal maldevelopment Appr r cent of all women that had a child born were treated gestagens during early pregnancy and slightly more used Primodos as a pregnancy test No harmful effect mbryonic development can be demonstrated

s is the third report on a linkage between drug ge and pregnancy outcome based on a prospec study carried out in Malmo during 1963–65 vious reports (10 11) dealt with two groups of gs which are often used during early pregnancy hopharmaca and antiemetic drugs The need to luate drug usage against the variability in inci ce and severity of symptoms at different out le of pregnancy was stressed This is perhaps more evident for one important group of drugs ch has been regarded as potentially teratogenic ocrine preparations Hormones are often given rder to adjust supposed abnormalities in the ocrine situation during the pregnancy which cause or be caused by disturbances in fetal elopment

ormones given to the mother can undoubtedly ct the embryo The masculinizing effect of cer gestagens on female fetuses is perhaps the known example This is described both from nal experiments and from clinical experience 7 20) During recent years the relationship be n the use of diethylstilboestrol during preg y and the development in the offspring of nal dysplasias and carcinoma during lescence has been much discussed (cf 6) Some tors have also suggested that the use of sex oids during early pregnancy can cause other types of malformations notably closure defects of the central nervous system (4 5—contradicted by 12 13 19) congenital heart defects consisting of transposition of the great vessels (14 16 18) and hypospadias (1 2) Special interest was then paid to hormones used as pregnancy tests most popular before the immunological pregnancy tests had come into common use It was recently suggested (8) that a relationship exists between oral contraceptive failure or other sex steroid treatment during early pregnancy and the birth of infants with congenital limb reduction defects One hundred and eight women gave birth to such infants—six had become pregnant in spite of oral contraceptives and nine had had other sex steroid treatments as a supportive measure (six) or as a contraceptive accidentally started after conception (three) Among 108 mothers of normal infants one had a contraceptive pill failure and three had received sex steroid therapy during early pregnancy

MATERIAL AND METHODS

The information on which this study is based was collected in a prospective study of 6376 pregnancies described in some detail in the first paper of this series (10)

RESULTS

A *Gestagens*

Fig 1 compares the use of gestagens during the different months of pregnancy in two groups of pregnant women those who will later have a miscarriage and those who will have an infant born In the latter group of 5753 women the highest incidence of gestagen exposure was found in the third gestational month 103 women=1 8% then had

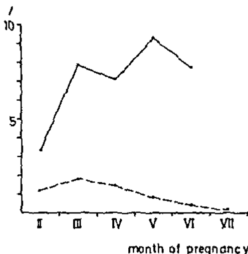


Fig 1 Percentage of women using gestagen preparations during different months of pregnancy Comparison between women who will miscarry (—) and women who will have an infant ( )

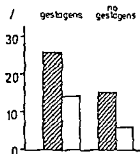


Fig 3 Percentage of women who miscarried Comparison between women with and without gestagen therapy Hatched column marks women who reported early bleeding during the present pregnancy empty column marks women who did not report such bleeding during the present pregnancy

been given such drugs Among these 92 women had an infant that did not survive—none of the women had been given gestagens during the third month 194 infants had major malformations 3 (=1 5%) of the mothers had been given gestagens during the third month

When the group of women who will later miscarry is compared with the above-mentioned group the gestagen usage is obviously much higher (Fig 1) During the third month 24 of the 305 women who later aborted were taking gestagens ($\chi^2=52\ 1$ at 1 d f $P<0\ 001$)

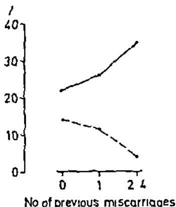


Fig 2 Percentage of women who miscarry according to number of previous miscarriages Comparison of women who reported early bleeding during the present pregnancy (—) and women who did not report such bleeding ( ) All women were given gestagens during the first trimester

The obvious explanation for this is that gestagens were given in an effort to prevent a threatened abortion by correcting a supposed progesterone deficiency Among 200 pregnancies in which gestagens were administered bleeding had occurred previously in that pregnancy in 81 and there had been a previous miscarriage in 105 (in [illegible] of these more than one previous miscarriage) Both previous miscarriage and bleeding during the present pregnancy had occurred in 36 cases In the remaining 50 instances the reason for gestagen administration is not clear

Fig 2 shows the risk of miscarriage in a pregnancy treated with gestagens according to presence of bleeding during the pregnancy and according to previous miscarriages The Figure shows that bleeding is the more important prognostic factor a previous miscarriage only increases the risk in the presence of bleeding during the present pregnancy Fig 3 compares the miscarriage rates with and without gestagen treatment in the presence and absence of previous bleeding during the pregnancy The higher miscarriage rate in the gestagen treatment group is probably because this group is selected as a high risk group If this risk is to any extent reduced by giving gestagens cannot be decided from these figures

Among 5002 women who gave birth to [illegible] malformed infants 98 had been treated with gestagens at some time during the first trimester i e appr 2% Among 551 women whose [illegible] had only minor malformations 9 had been treated with gestagens slightly below 2% Among the women who had infants with major malformations

e I *Summar\ of pregnancies \\ here Prımodos ısed durıng the second month of amenorrhoea pregnanc\ dıagnosıs test*

ıancy outcome	Total no of women	No usıng Prımodos	% usıng Prımodos
ırrıage	448	15	3 3
ed abortıon	154	13	8 4
of ınfant	5 753	128	2 2
ıal ınfant	4 910	107	2 2
ınfant	9?	1	–
r malformatıon	551	16	2 9
r malformatıon	194	4	2 1

treated wıth gestagens 15 ınfants had ›spadıas and 11 had major malformatıons of the S but none of these mothers had used ıgens

ıere was no assocıatıon between gestagen ıent and gestatıonal age at bırth or weıght at Five of the non malformed ınfants of ıen treated women were born more than 2 ı before the expected date compared wıth the pated number of seven Three were born more two weeks after the due date whereas 3 to 4 expected to do so Among the ınfants born ıen 38 and 42 weeks of pregnancy the weıght butıon was ın the expected range less than 2 5 (expected 1 9) 2 5–3 kg 8 (10 2) 3–3 5 kg 36 ı 3 5–4 kg 29 (31 5) over 4 kg 29 (31 5)

B *Prımodos*

›dos ıs a drug contaınıng norethısterone and ›loestradıol and was much used as a means of osıng pregnancy In the present serıes ıt was ı to 156 women durıng the second month of ıancy—most of them were gıven ıt to dıagnose ıancy Table I presents the outcome of the ıancy ın relatıon to Prımodos usage It ıs obvı hat the group of ınduced abortıons contaınıng ınted pregnancıes shows a hıgh ıncıdence of odos usage ($\chi^2=12\ 9$ at 1 d f $P<0\ 001$) In the p of future mıscarrıages a slıghtly ıncreased ence ıs also seen—thıs agrees wıth the hıgh ıency of unwanted pregnancıes ın thıs group ably hıdıng a number of ınduced abortıons (cf

C *Other hormones*

rogens and anabolıc steroıds were gıven to 65 ıen durıng the second month of pregnancy and

ıorticosteroıds to 11 A hormone of any type was gıven durıng the fırst trımester to 238 of the 6 376 women ıncluded ın the present study ı e 3 7% The only hormone where an obvıous assocıatıon wıth pregnancy aberratıons could be demonstrated was ınsulın Among 15 dıabetıc women who were on ınsulın two had a mıscarrıage sıx had a normal lıvıng ınfant three had normal ınfants that dıed perınatally one had an ınfant wıth a mınor malfor matıon and three had ınfants wıth major malforma tıons (one wıth gut atresıa two wıth multıple malformatıons)

DISCUSSION

In spıte of the possıble deleterıous effects on the fetus of certaın hormones admınıstered durıng preg nancy 3 7% of the women ıncluded ın the present study reported that they had used hormonal drugs durıng the fırst trımester ıncludıng the organogene tıc perıod One large group of them were treated wıth gestagens maınly ın order to prevent a threatenıng abortıon No effect was obvıous from thıs poınt of vıew whıch agrees wıth the now pre vaılıng vıew on the lack of effect of gestagen therapy for thıs purpose In a double blınd well controlled study of the effect of gestagen ın threatened abortıon ın a serıes of 260 cases no dıfference was found ın the outcome of the preg nancy between patıents treated wıth gestagen and patıents treated wıth placebo (3)

No teratogenıc effect of the gestagens could be demonstrated It ıs of a specıal ınterest that none of the 15 women who gave bırth to ınfants wıth hypospadıas had used gestagen preparatıons—thus none of the 112 ınfants whose mothers got gestagens had hypospadıas Thıs does not exclude a teratogenıc effect of gestagens general or specıfıc for hypospadıas but ıf such an effect exısts ıt must be relatıvely weak

The same holds true for the hormonal prepara tıons used for pregnancy dıagnosıs ın our study ıllustrated by Prımodos None of the 128 women *who used Prımodos durıng the second month of* pregnancy had an ınfant wıth hypospadıas and the number of ınfants wıth major malformatıons ın general was not ıncreased ın thıs group The fıgures do not exclude a teratogenıc effect of such hormone preparatıons but they gıve no support for ıt

The maın argument for an assocıatıon between the use of gestagens and the development of

hypospadias is the work presented by Aarskog In his first report (1) four women among 80 who gave birth to an infant with hypospadias had received gestagens and another woman had used Primodos In his second report (2) the series had been increased by 20 to a total of 100 One further Primodos user was then included and three further women who had received gestagen therapy The sampling principles for the extended series are not clear but it is noteworthy that the incidence of hormone users is higher in that series than in the first reported series (4/20–5/80) No control series was presented in any of the studies so it is not possible to know if the incidence of hormone users described is higher than that expected Local variations are probably large both with regard to gestagen usage for threatening abortion and to the use of hormonal pregnancy diagnosis tests In the present study approximately 2% of all women who later had an infant had taken Primodos A corresponding figure given from Atlanta (17) is 10%

A weak correlation can be found between the use of sex steroids and the birth of malformed infants without any cause and effect existing Gestagens were in the present study prescribed more often if bleeding had occurred early during the present pregnancy or if previous reproductive failure had occurred than if no such complicating factor existed Both these problems are associated with the birth of more malformed infants than normal

The only endocrine treatment which showed a clear cut correlation with pregnancy outcome is insulin This is obviously due to the diabetes and not to the drug The pregnancy wastage recorded in this group is high According to Möller (15) the perinatal mortality should not be much increased among infants of diabetic mothers if the latter are supervised closely from early pregnancy and if their blood sugar levels are carefully controlled

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PHOSPHOLIPID CONCENTRATIONS IN AMNIOTIC FLUID FROM DIABETIC PREGNANT WOMEN

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ract Amniotic fluid phospholipid concentrations ured in 104 samples from 65 diabetic patients have related to gestational age the state of diabetes ac ing to White s classification and the development of spiratory distress syndrome (RDS) There is statisti significant evidence of accelerated surfactant pro- on in White classes D F from 34 to 37 weeks gesta Classes A B C have phospholipid concentrations ignificantly different from a reference series RDS rred in 6% and was frequently associated with ma phospholipid concentrations There was a significant lation between low Apgar scores and subsequent lopment of RDS

is long been recognized that newborn infants of hers with diabetes mellitus have a higher inci e of RDS than infants of non diabetics of the e gestational age despite a high birthweight (2 several authors have proposed this to be due to layed pulmonary maturation as measured by a ly in the rise of phospholipid concentrations in iotic fluid from 34 weeks gestation (8 10 14 Gluck (8) has found that in the diabetic state re is a retardation of surfactant development in te s classes A B C and accelerated maturation lasses D F Several reports have indicated that thin/sphingomyelin (L/S) ratio determinations be of doubtful prognostic value in diabetic gnancies This is based on the occasional de opment of RDS despite mature L/S ratios (4 6 2 16 18)

he purpose of the present study has been to estigate the maturation of the fetal pulmonary factant system in diabetic pregnancies as meas d by the amniotic fluid lecithin concentrations L/S ratios and to examine the relationship be en these parameters and the development of S Certain other factors which might influence the surfactant system and respiratory function have also been studied

MATERIAL AND METHODS

109 samples of amniotic fluid from 67 diabetic pregnant women were collected by transabdominal amniocentesis or at the time of caesarean section during a three year period from 1971–74 Antenatal care during the last trimester and delivery took place at the Department of Obstetrics and Gynaecology Rikshospitalet All neonates were immediately transferred to the Department of Pediatrics Two samples from a child with multiple malformations who died during labor were excluded together with three samples from one patient with un known gestational age so that 104 samples were left for analysis 94 samples were analyzed by the method previ ously published by Lindback et al who had used un centrifuged amniotic fluid which gives higher lecithin con centrations and L/S ratios (10 11) The lecithin concentra tions are given as micromoles in 100 ml amniotic fluid 59 samples were analyzed by Gluck s method as follows Centrifugation of the amniotic fluid at 1050 g×5 minutes Lipid extraction in methanol/chloroform 2 2 4 The chloroform phase was dried under N followed by cold acetone precipitation this layer chromatography with silica gel H with 5% ammonium sulphate charring and cromoscanning 49 samples were analyzed by both methods

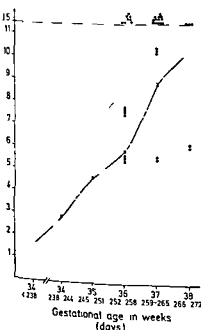
Gestational age has in the text been given in terms of weeks meaning completed weeks i e 39 weeks=273–279 days The phospholipid concentrations from the diabetic pregnancies have been compared at weekly intervals with a reference series consisting of rhesus immunized women with rhesus negative babies or with no pathological hemolysis (i e Liley Zone I) and patients with normal pregnancies For the patients included in the reference series there should be no pathological factors influencing the surfactant production

The Wilcoxon two-sample test the Wilcoxon van Eltern test and the Fisher Irwin test have been used for statistical analysis The significances given (*P*) are for two sided tests

Table I *Lecithin concentrations in μM/100 ml amniotic fluid and lecithin/sphingomyelin (L/S) r… maternal diabetes of classes ABC and DF compared with non diabetic controls at different ges ages*

Gestational age in weeks (days)	ABC (Lecithin)	DF (Lecithin)	Control (Lecithin)	ABC (L/S ratio)	DF (L/S ratio)	Control (L/S ratio)
<34	4.37	0.67	0.51	6.94	2.03	0.61
<238		1.69	0.56		3.19	1.22
		2.47	0.70		3.80	1.77
			0.89			1.44
			1.04			1.63
			1.56			1.67
			1.67			2.41
			3.57			3.97
Median		1.69	0.97		3.19	1.54
34	1.21	3.36	0.53	0.55	4.10	0.74
238–244		3.52	0.70		4.63	1.10
		3.84	1.27		4.86	2.33
		6.50	1.47		10.00	2.40
			2.71			3.49
			2.86			4.11
			4.37			7.80
			7.02			8.07
Median		3.68	2.09		4.75	2.94
35	1.52	3.12	1.43	1.45	2.64	2.80
245–251		3.78	2.12		3.63	3.44
		5.21	2.48		4.97	3.93
		5.64	2.70		5.27	4.36
		6.54	3.43		6.06	4.74
		6.62	3.49		6.86	6.07
		6.83	3.70		7.97	6.37
		7.05	4.54		8.95	10.09
		7.43	4.88		9.36	10.37
		9.02			11.00	
		9.54			11.16	
		13.62			11.36	
Median		6.73	3.43		7.39	4.74
	1.78	3.32	1.30	1.68	4.77	2.55
–258	2.59	5.00	1.90	1.84	5.44	3.30
	3.07	5.89	3.00	5.50	6.93	3.84
	3.63	6.38	4.25	5.70	7.58	3.84
	4.24	6.87	4.82	6.74	7.85	4.87
	7.70	7.48	5.12	6.42	8.48	5.17
	9.00	7.92	6.30	7.49	9.03	5.88
	9.44	11.30	6.35	7.67	9.25	6.88
	11.86	11.60	7.38	15.01	9.67	7.97
	14.50	12.30	8.22	21.87	10.00	10.08
	16.40	12.61	8.58	21.95	13.14	11.4
		15.03	10.14		15.00	13.86
		16.52	14.28		15.76	17.49
		17.00			17.17	
		19.52			19.78	
		19.78			36.00	
		20.16			44.36	
Median	7.70	11.60	6.30	6.42	9.62	5.88
37	2.95	2.44	4.16	2.49	3.09	5.80
259–265	4.19	2.61	4.41	4.89	4.08	6.24
	4.43	4.45	4.58	5.40	5.49	6.37
	5.68	4.83	4.64	5.68	6.11	6.60
	6.24	6.34	6.70	6.86	7.83	7.11

ational age eks (days)	ABC (Lecithin)	DF (Lecithin)	Control (Lecithin)	ABC (L/S ratio)	DF (L/S ratio)	Control (L/S ratio)
	7 98	7 14	6 94	10 06	8 03	7 37
	9 28	10 06	7 69	10 73	9 27	8 50
-	9 86	11 17	7 93	10 30	9 47	8 81
	9 90	12 30	8 67	10 76	10 47	8 94
	9 96	14 43	8 80	11 96	11 84	8 95
	10 03	16 70	9 93	13 46	12 33	9 51
	10 55	20 13	10 68	13 72	19 42	10 53
	10 86	37 78	11 60	13 75	39 77	12 57
	11 02		12 22	14 10		13 03
	12 76		12 24	15 37		14 07
	13 99		16 52	15 90		26 2
	14 57			16 01		
	15 40			17 91		
	16 76			19 54		
ian	9 96	10 06	8 30	11 96	9 27	8 88
	3 33	4 05	2 13	6 17	4 93	1 78
[illegible]	5 33	5 00	2 54	7 51	5 33	4 70
	9 78	5 03	4 74	13 40	5 62	5 71
	11 10	5 68	7 16	13 67	6 04	9 06
	11 48	7 58	8 40	17 08	7 58	9 78
	14 61		9 36	20 01		10 7
			13 47			11 51
			18 10			14 00
			18 22			15 48
			18 96			16 41
			24 78			18 06
ian	10 44	5 03	9 36	13 59	5 62	10 77



1 Amniotic fluid lecithin/sphingomyelin (L/S) ratios 94 samples from pregnant diabetic women related to tational age ● One sample from a diabetic dian values for the diabetics —— Median values for 65 non-diabetic controls

The diabetics have been divided into two groups according to White s classification One group consists of classes A B C and the second group of classes D F which had diabetic retinopathy and/or nephropathy The data from these two groups have been evaluated and compared with each other and with the reference series mentioned above

The results from the diabetic samples obtained within one week of delivery have been related to the development and severity of the RDS These findings have been compared with a second reference group consisting of rhesus immunized and normal patients The assessment of *the respiratory function of the newborn has been as previ*ously published (10) In addition respiratory distress requiring supplemental O_2 for less than 24 hours had been defined as transitory

RESULTS

Fig I shows the calculated L/S ratios from 94 diabetic samples related to gestational age The data for lecithin concentrations and calculated L/S ratios are listed in Table I The median values for both parameters in the total diabetic group are higher from <34–37 weeks gestation than the median values for the reference group whereas at 38 weeks the median values are lower than at 37 weeks and also lower than the reference group The differ

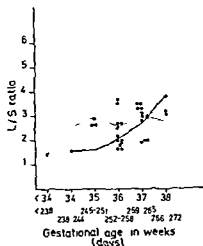


Fig 2 Amniotic fluid lecithin/sphingomyelin (L/S) ratios *in 59 samples from pregnant diabetic women (Gluck s* method) related to gestational age ● One sample from a diabetic median values for the diabetics —— median values for 41 non-diabetic controls

ence for the L/S ratios<34 weeks gestation is marginally significant $P=0\ 05$ by the Wilcoxon two-sample test but there is no significant difference between the groups at weekly intervals from 34–38 weeks gestation However combining the data from <34–37 weeks gestation gives a difference which is highly significant $P<0\ 001$

Fig 2 shows the L/S ratios in 59 randomly unselected diabetic samples analyzed by Gluck s method 49 of these samples are included in Fig 1 ne median values for the diabetics are higher from to 36 weeks than the reference group Otherwise results demonstrate the same tendency as seen n Fig 1 with generally lower L/S ratios due to the methodological difference

In Fig 3 the patients have been divided into two groups according to White s classification A B C in one group and D F in the other The median values for classes A B C—39 samples—increase from 36–38 weeks gestation and are higher than the corresponding values for the reference group The difference is not significant We have no results for classes A B C prior to 36 weeks gestation The median phospholipid concentrations in classes D F rise steeply from <34–36 gestation and are markedly higher than the corresponding values for both the reference group and classes A B C At 36 weeks gestation there is a significant difference for the L/S ratios of classes D F vs controls $P<0\ 05$ For the period <34–36 weeks the difference is highly significant $P<0\ 001$ At 37 weeks the median values for classes D F are slightly lower at 36 weeks and at 38 weeks they are markedly lower than both the controls and the A B C groups Statistical analysis of the differences between classes D F and A B C respectively controls at 38 weeks were considered invalid because these patients represent a selected group

The 65 diabetic patients included in the study gave birth to 66 infants Eleven of these developed RDS (~17%) In addition 6 infants had transitory respiratory distress Altogether 26% of the infants had some symptoms of respiratory distress but none died and only one child was considered to have a lifethreatening illness

Figs 4 and 5 present phospholipid concentrations in samples from 55 non-diabetic patients delivered within one week of delivery In this group the clinical picture of transitory RDS has not been reported Nine infants had RDS and all had lecithin concentrations <4 6 μM/100 ml and L/S ratios <5.0 All infants with higher lecithin concentrations had normal respiratory function

Figs 6 and 7 present the lecithin concentrations and the calculated L/S ratios in infants of diabetic mothers obtained within

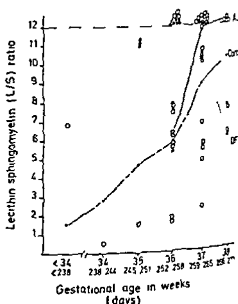
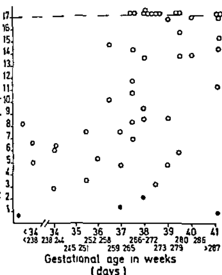
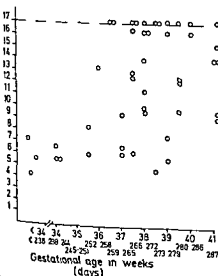


Fig 3 Amniotic fluid lecithin/sphingomyelin (L/S) ratios in 93 samples from pregnant diabetic women (one patient unclassified) related to gestational age O One sample from a diabetic classes A B C ● one sample from a diabetic classes D F —— median values for classes A B C median values for classes D F — — median values for 65 non-diabetic controls



4 Amniotic fluid lecithin concentrations obtained ...in one week of delivery from 55 non-diabetic patients ...ed to gestational age O No RDS ● RDS

...k of delivery For the remaining 7 infants in ...group the interval between amniocentesis and ...very was more than one week The majority ... collected at caesarean section We have pre...usly found RDS constantly to be associated ...h low phospholipid concentrations In this dia-



5 Amniotic fluid lecithin/sphingomyelin (L/S) ratios ...tained within one week of delivery from 55 non-diabetic ...tients related to gestational age O No RDS ● RDS

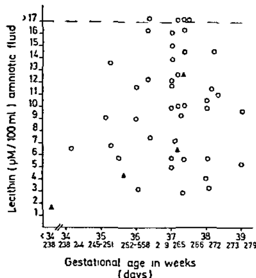


Fig 6 Amniotic fluid lecithin concentrations obtained within one week of delivery from 58 diabetic patients related to gestational age O No RDS ▲ transitory RDS ● RDS

betic series RDS occurred even with very high phospholipid concentrations Ten patients with lecithin concentrations >4 6 μM/100 ml and 7 patients with lecithin concentrations <4 6 μM/100 ml developed RDS Of these there were 12 with a L/S ratio >5 0 and 5 with L/S ratio <5 0

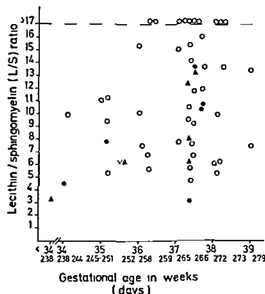


Fig 7 Amniotic fluid lecithin/sphingomyelin (L/S) ratios obtained within one week of delivery from 58 diabetic patients related to gestational age O No RDS ▲ transitory RDS ● RDS

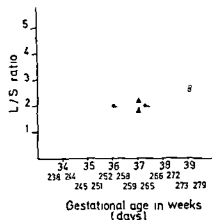


Fig 8 Amniotic fluid lecithin/sphingomyelin (L/S) ratios obtained within one week of delivery from 33 diabetic patients (Gluck s method) related to gestational age O No RDS ▲ transitory RDS ● RDS

Fig 8 illustrates the L/S ratios in 33 of the diabetics analysed by Gluck s method These were unselected samples obtained within one week of delivery There were 7 cases of RDS and 2 additional cases of transitory RDS Eight of these had L/S ratio ≥2 0 In neonates from non diabetics we have hitherto not seen RDS with a ratio ≥2 0 by this method

The relationship between the mode of delivery and respiratory function is difficult to assess since the majority (~80%) were delivered by caesarean section The proportion of RDS was approximately he same with either route of delivery

Table II shows the Apgar scores for 61 neonates There is a preponderance of low Apgar scores in the group with RDS The Fisher Irwin test demonstrates a highly significant correlation between asphyxia at birth and subsequent clinical outcome $P \sim 0\ 01$ with the two sided test

In a preliminary study of the maternal urinary estriol values there seemed to be no obvious correlation either to phospholipid levels or respiratory function in the newborn We were also un[able to] find any relationship between birthweight [and] phospholipid concentrations at any given ge[statio]nal age The incidence of RDS was the same [in both] sexes

Nearly all diabetics in this study were [well] controlled especially during the last trimeste[r The] importance of poor maternal control with res[pect to] RDS is therefore impossible to assess in this [mate]rial

There is a slight over representation of [boys in] the offspring of diabetics in classes D F [but the] difference is not significant

Table II *Relationship between Apgar scores and subsequent RDS*

Apgar scores	No of patients	RDS	No RDS
3–7	11	7	4
8–10	50	10	40

DISCUSSION

In the present study there is no general evidence [of] delayed maturation of the pulmonary surf[actant] system in diabetic pregnancies On the contr[ary] from <34–37 weeks gestation there are significa[ntly] higher phospholipid concentrations in the sam[ples] from the diabetic patients than in the referen[ce] group (Figs 1 and 2) The results at 38 weeks [are] inconclusive It is partly a selected group of pa[tients] where delivery was postponed because of l[ow] phospholipid concentrations in earlier sam[ples] Whitfield et al (18) found that the normal term[inal] rise in the L/S ratio did not occur in approx[imately] one third of the diabetic patients Evidently the[re is] a delay in the normal terminal rise of the L/S rat[io in] some of our patients but we have observed th[is in] other groups of patients and even in pregnan[cies] considered to be normal Whitfield et al also [noted] a steep fall in the L/S ratio in three patients A [similar] fall was observed in two of our patients at this s[tage] of gestation The extent to which low val[ues in] classes D F are due to a fall or a delayed matura[]tion will be examined in further studies

It is seen in Fig 3 that nearly all samples ob[tained] before 36 weeks gestation are in White groups D F Our findings of a highly significant difference be[]tween groups D F and the reference series strong[]ly supports Gluck and Kulovich s theory of acce[ler]ated mautration of the surfactant system in the[se] groups Their suggestion of retardation in class[es] A B C is however not in accordance with [our] results For these groups we find a steady incre[ase] in the phospholipid concentrations parallel to the reference group The median values are higher th[an] in the reference group but the difference is n[ot]

ant This is in agreement with other reports

ie present time there is general acceptance iture phospholipid concentrations in amnio- l indicate minimal risk of RDS in the new Vith our method mature lecithin concentra .re >4 6 μM/100 ml and L/S >5 0 With ; method delivery is considered safe with an io ≥2 0 In our reference group (Figs 4 and : is no case of RDS among those with mature In the diabetic group however there are cases of RDS with mature concentrations 5 7 and 8) The occasional occurrence of i infants of diabetic mothers despite mature tios has been observed by several authors is been regarded as exceptional but the fre ' with which it occurred in our group makes it s that mature values are no guarantee against tory distress

much as our measurements have been made niotic fluid it is interesting to note that on et al (1) found normal lecithin content rface tension properties in the lungs of three of diabetic mothers who died of hyaline ane disease (HMD) In their study this was ional and they suggested that the HMD seen its of diabetic mothers was of a unique kind ilso found evidence that these infants could e exceptionally well endowed with surfac

resent we have no adequate explanation for ccurring in the presence of ample surfactant iportant factor is asphyxia at birth as demon l by our finding of a highly significant rela ip between low Apgar score and the subse development of RDS This confirms the find ade in other studies (3 4 7 13) On the other ome infants with mature phospholipid con tions and no asphyxia at birth developed In our series there were no deaths from RDS should be pointed out that the majority were l to be mildly affected only It is our expe that the condition of the newborn has im l considerably since stricter control of the ial diabetes was introduced Both mortality orbidity from RDS have been reduced Con ig the paradox of RDS developing despite ate phospholipid concentrations it is possible ven stricter control of the maternal diabetes improve metabolic and circulatory factors in wborn of importance for respiratory function

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SECONDARY AMENORRHOEA AND ORAL CONTRACEPTIVES

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act Eighty seven cases of secondary amenorrhoea re than 6 months duration developing after treat with oral contraceptives (group I) were compared 27 cases of secondary amenorrhoea not preceded by nent with combined tablets (group II) The two s were collected during the same period The aver ge of the patients was 4 years higher in group I than in II Oligomenorrhoea had previously occurred in of group I and in 46% of group II Pronounced pre sing factors such as psychogenic trauma and stress or without considerable change in body weight were ntered in 26% in group I and 56% in group II The nce of increased urinary output of 17 keto steroids togenic steroids and of hirsutism was slightly higher up II The percentage of eosinophilic cells in vaginal ings was low in 70% in group I as compared with in group II Spontaneous return of pituitary-ovarian ion occurred in 40% in both groups Patients recov spontaneously in group I presented a maximum g the first few months followed by a steady and uniform decline Spontaneous recovery in group II nore or less independent of time It seems reasonable li ve that oral contraceptives did promote or contri to the development of secondary amenorrhoea in t 50% representing cases with various predisposing rs A causal relation between oral contraceptives and dary amenorrhoea was indicated in the remaining because of perfectly normal ovarian function before nent and absence of predisposing factors

tment with tablets containing oestrogens and agens (oral contraceptives) brings about within w months a considerable suppression of pitui gonadotrophic hormones and of ovarian en ine function When the treatment is discon ed endocrine activity is re-established im iately in most cases Some delay is seen in a or percentage and secondary amenorrhoea de ps in a few cases The first case of secondary norrhoea following treatment with oral con eptives was published in 1966 (13) Since then a large number of reports have appeared in which the relation between oral contraceptives and secondary amenorrhoea is discussed The fact that this rela tion is still obscure prompted us to approach the problem in a comparative study of two groups of patients with secondary amenorrhoea the first group having used oral contraceptives while the second had not received any preceding hormonal treatment

MATERIAL AND METHODS

The series studied included 87 cases with secondary amenorrhoea starting immediately following treatment with oestrogen gestagen tablets (group I) and 227 cases with secondary amenorrhoea not preceded by hormonal treatment (group II) All patients were referred to The State Maternity Hospital University of Aarhus It seems reasonable to believe that most if not all cases occurring in the surrounding area a city with a population of about 250 000 inhabitants were seen In addition the series in cluded a number of cases from more distant areas referred to us by gynaecological departments consultants and general practitioners

Secondary amenorrhoea was defined as amenorrhoea of more than six months duration including all cases ir respective of the menstrual pattern preceding the amenorrhoea Cases due to obvious organic disease were not included in any of the two groups which were col lected from January 1966 to July 1972

On admission to the hospital all the patients were sub- jected to an endocrine examination including determina- tion of urinary output of 17 keto steroids 17 ketogenic steroids and total gonadotrophins by the routine methods applied by the Danish State Serum Institute Abnormal results were confirmed by repeated examinations In ad dition basal metabolic rate PBI and tri iodo thyronine were measured The percentage of eosinophilic cells in vaginal scrapings was assessed in three examinations Radiological examination of the sella turcica and testing of the visual fields were carried out Biopsy of the en- dometrium and chromosome studies were not performed routinely

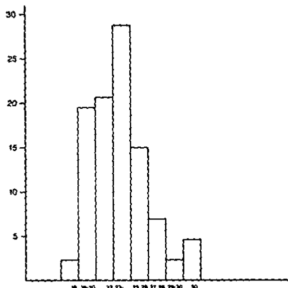


Fig 1a The distribution of patients in group I on the basis of age at the onset of amenorrhoea

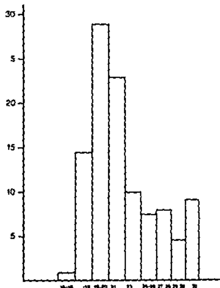


Fig 1b The distribution of patients in group II o basis of age at the onset of amenorrhoea

RESULTS

A few facts concerning oestrogen gestagen treatment will be considered before a detailed description of the two groups is given

The indication for treatment with combined tablets was mainly a demand for contraception (69%) or irregular usually infrequent periods (28%) In two cases treatment was instituted because of dysmenorrhoea The composition of our series is fairly similar to that reported by other authors (e g 6 9) During treatment perfectly regular withdrawal bleeding occurred in 92% The treatment was discontinued because the patients wanted to become pregnant (23%) because of side effects (22%) and because it was supposed to be reasonable to stop for a while (19 5%) wh no definite reason was stated in about one th the cases

The age distribution of the two groups (Fig disclosed a significant difference ($p = 0.01$) the av erage being 4 years higher in group I th in gr II The body weight of the patients is illustrat Fig 2 which is based on weights and he cording to Danish standards (life insurance t The distribution is fairly uniform and both g include a considerable number of cases bel ideal

No conspicuous difference was demonstrat tween the age at the menarche (Fig 3) in the groups although the average was slightly hig

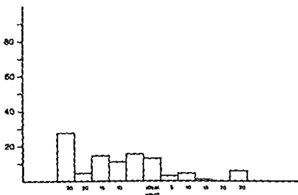


Fig 2a The distribution of patients in group I on the basis of weight and height

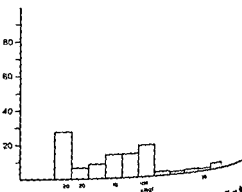
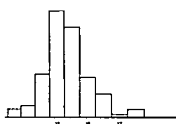


Fig 2b The distribution of patients in group II o basis of weight and height



[T]he distribution of patients in group I on the basis [of the age] at the menarche

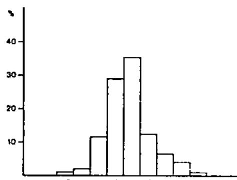


Fig 3b The distribution of patients in group II on the basis of the age at the menarche

[The menstrual pattern preceding sec[ondary] amenorrhoea was compared oligomenor[rhoea be]ing defined as vaginal bleeding occurring at [intervals] of 45 days or more The percentage of [women with] normal periods before the use of oral con[traceptiv]es was 55 as compared with 50 in group [II Oligo]menorrhoea was present in 30% in group I [and ...]% in group II The difference in the occur[rence o]f oligomenorrhoea is significant ($p=0.05$) [Th]e relation between psychogenic factors and [secondar]y amenorrhoea has been demonstrated by [a numbe]r of investigators (for references see 6 7) [In the] present series all cases with psychogenic [factors w]ere recorded provided a close chronologi[cal rela]tionship was demonstrated between pro[longe]d psychogenic trauma or massive stress with [or with]out a major change in body weight for ex[ample d]ue to divorce a temporary stay abroad or [preparatio]n of reading for an examination Although [such a] record includes subjective factors it should [be poss]ible to avoid bias when both groups are [assesse]d according to the same criteria and by the [same in]vestigator A predisposition of this nature [was pre]sent in 26% of the patients in group I and in [...] group II The difference is significant [($p<0.0$]25)

[Galac]torrhoea defined as a complaint of spon[taneous] milk like secretion from one or both [breasts] occurred in one case in group I and in four [in] group II Figures presented in the literature [vary w]ithin wide limits This variation may be due [to geog]raphical differences (5 10 14) although it [is re]asonable to assume that differences [may] depend on a search for and inclusion of [cases] disclosed by manual expression of the [breasts] The incidence as assessed by this approach is considerable in parous women and independent of treatment with contraceptive drugs (14)

A detailed discussion of the treatment and prognosis in the two groups is not appropriate in this context because the approach to treatment was not absolutely identical Patients with secondary amenorrhoea occurring after the use of oestrogen gestagen tablets were followed without any treatment being given apart from those complaining of sterility whereas the attitude towards treatment was more liberal in cases belonging to group II The incidence of spontaneous recovery of pituitary ovarian function was 40% in both groups representing minimum values based on follow up periods of varying lengths and calculated on the total number in each group without respect to cases dropping out of the follow up study The intervals between the onset of secondary amenorrhoea and the first bleeding indicating recovery are presented in Fig 4 which shows a substantial difference between the two groups

Reports on the return of ovarian function after secondary amenorrhoea are contradictory on several points The length of the period justifying the use of the term varies in individual papers Particular attention is usually not paid to cases due to organic disease Many of the series published comprise only a limited number of cases and the follow up periods are often rather short Very good results were obtained in a Swedish series (8) with spontaneous remission in 69% of 178 cases of secondary amenorrhoea developing after hormonal treatment with follow up periods up to 39 months

Finally it should be mentioned that in our series the percentage of patients in whom spontaneous return of ovarian function occurred after treatment

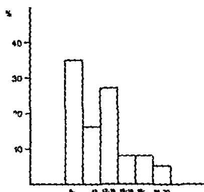


Fig 4a The distribution of patients in group I on the basis of the first bleeding indicating re-establishment of ovarian function

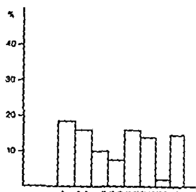


Fig 4b The distribution of patients in group II [on the] basis of the first bleeding indicating re-establi[shment of] ovarian function

with oral contraceptives was roughly alike in patients who had a perfectly normal menstrual pattern and in those with oligomenorrhoea before treatment was started However the tendency to recovery in group I depended to a certain extent on the number of years which had elapsed between the menarche and the start of treatment with combined tablets in women who started 5 years or more after the menarche ovarian function was re established in 32% as compared with 42% in those who started less than 5 years after the menarche

DISCUSSION

The relation between treatment with oral contraceptives and the development of secondary amenorrhoea has been widely discussed The difference of opinion is reflected in the terms post contraceptive amenorrhoea (9) and the oversuppression syndrome (1) On the other hand many authors question the relation or completely reject any sort of relationship calling attention to the occurrence of functional amenorrhoea in the population although the incidence is so far questionable (12 15) Attention has also been directed to psychogenic factors and to the uniformity of all cases of secondary amenorrhoea as far as clinical prognostic and therapeutic aspects are concerned although systematic comparisons of cases with and without preceding treatment with oral contraceptives do not seem to be available

Within a few months treatment with oral contraceptives produces a considerable depression of pituitary and ovarian function presumably due to inhibition of the release of the hypothalamic releasing factor When treatment is di[scontinued ovarian func]tion is promptly re established in about 75% [...] certain extent depending on the types of [...] administered and the composition of [...] studied The great majority of the remaining [...] present delayed periods ovulatory or anovulatory quite often with some irregularity A few [...] experience amenorrhoea of more than 6 m[onths] duration The frequencies of secondary [amen]orrhoea observed in series comprising [...] 2000 to 20000 cases vary from 2–3/1000 [...] 7/1000 (10) although higher figures have been [reported] in small series for example 2 7% (2) In conclusion it seems reasonable to consider the clinical p[...] described as a spectrum from immediate r[...] on the one hand to long standing amenorrhoea on the other

The incidence of secondary amenorrhoea [in the] total population has not been established Investigations related to this problem have been based [on] selected samples of the population almost [all of] whom had been exposed to stress of a varying [na]ture (3 4) Accordingly it is not possible to de[termine] whether secondary amenorrhoea following [oral] contraceptive treatment occurs with an [incidence] differing from that in fertile women in general [It is] obvious that cases of secondary amenorrhoea [after] the use of oral contraceptives will involve [an in]creasing percentage of the total number [in the] course of time The series presented here [does] allow a comparison between the in[crease in] percentage year by year and the increase [in the] use of oral contraceptives About 25% of the [to]tal number occurred after treatment [with es]trogen gestagen tablets but this percentage [rep]resents a minimum value because the col[...]

was started in 1966 the very year when oral iceptives were introduced in this country ver it must be stressed that the majority of itients came from an area with a considerable er of institutes of higher education which im hat the basic series contained a comparatively iercentage of young and very young women ondary amenorrhoea which is not due to or disease is generally monosymptomatic Thus s not seem reasonable to question the im ice of oral contraceptives as a predisposing just because the clinical appearance of sec y amenorrhoea is similar to the control group letailed analysis of the findings in the two s disclosed some minor and a few major dif es The average age in group I was four years r than in group II Predisposition such ychogenic trauma stress and considerable e in body weight occurred in 26% in group I mpared with 56% in group II Furthermore II included more cases with an increased y output of 17 keto steroids and 17 ketogenic ds and rather more hirsute patients In addi he percentage of eosinophilic cells in the vag rapings was 46 in group I and 20 in group II omparison of the case records disclosed that erage age at the menarche was slightly higher up II Oligomenorrhoea during the year pre g treatment with oral contraceptives occurred % as compared with 46% during the year ding amenorrhoea in patients in group II

r reasons already specified the two groups not compared as regards the course of the se in general the treatment employed or the s of treatment Making a reservation for the ns mentioned it must be stressed that 40% of groups experienced spontaneous recovery recovering after treatment with oral con ptives presented a maximum during the first nonths followed by a steady and rather uni decline As far as group II is concerned aneous recovery was more or less independ f time

ng attention to the differences mentioned be groups I and II it seems reasonable to as that oral contraceptives promote or contri velopment of secondary amenorrhoea the same predisposing factors as patients with secondary amenorrhoea which been preceded by hormonal treatment of this nature may be enough to explain the development of secondary amenorrhoea in about 50% of cases occurring after treatment with oral contraceptives As far as the other 50% are concerned the presence of perfectly normal pituitary ovarian function before treatment the abscense of predisposing factors and the close time relation between discontinuation of treatment and secondary amenorrhoea are suggestive of a causal relationship Secondary amenorrhoea may be re garded as an extreme type of reaction in the pattern seen during the period after stopping oral con traceptives This view is supported by a compari son between the fairly slight suppression of pituitary-ovarian function seen after sequential treatment the moderate suppression produced by combined tablets and the pronounced effect of treatment with gestagens administered by injection every third month The increasing degree of suppression is reflected by the endometrial reaction (11) and by the tendency to develop secondary amenorrhoea

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PLASMA HORMONE CONCENTRATIONS DURING THE MENSTRUAL CYCLE OF NORMAL CHINESE WOMEN

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ict The concentrations of progesterone estrogens zing hormone and follicle stimulating hormone were ired in samples of plasma taken frequently during J menstrual cycles in fourteen Chinese women of the menstrual cycles was characterized by mal changes which were comparable to those previ reported in Caucasian subjects

ormone profiles in normal cycles of Caucasian n have been well documented (1 4 6 7 9 11 owever there has only recently been a report concentrations of hormones during the men cycle of an Asian population (8) As a pre ite to establishing an ovulation induction imme we considered that it was essential to iine the concentrations of hormones in nor ienstrual cycles of women native to Singa In the present study progesterone estrogens izing hormone (LH) and follicle stimulating ne (FSH) were measured in fourteen normal y Chinese subjects

PATIENTS AND METHODS

d methods

en normal healthy Chinese women with regular ual cycle were studied All subjects were nullipar ɥeir ages ranged from 21 to 32 (mean 24 6) years was collected at the same time every day from day day 70 of the cycle before and after this period on was performed every other day The blood was rred from the syringe to a lithium heparin tube was centrifuged and the plasma removed Aliquots plasma were removed and stored at −20°C until ɟ be completed

of progesterone

was assayed in duplicate using a specific mmunoassay based on a previous report (2) The specific antiserum against progesterone used in the pres ent study was generated in sheep by the injection of 11 hydroxy progesterone hemisuccinate conjugated to BSA Plasma samples (0 5 ml) were extracted in duplicate with petroleum ether (30–40) The extracts were dried and dis solved in tris buffer (pH 7 8) containing 0 1% gelatin (1 5 ml) Duplicate aliquots (0 5 ml) of the extract in buffer were removed for assay Antiserum at a concentration of 1 1000 (0 1 ml) and tritiated progesterone (0 1 ml contain ing approximately 10000 dpm) were mixed with the sam ple After an incubation period of 18–24 hours at 0–4 C dextran coated charcoal was added to adsorb the free steroid The tubes were centrifuged for ten minutes in the cold and an aliquot of the supernatant (0 5 ml) was placed in a liquid scintillation vial containing 10 ml toluene based scintillation fluid with Triton X 100 The radioactivity was determined in a Nuclear Chicago Mark II Liquid Scintilla tion Counter The progesterone concentration was calcu lated from standard curves and were corrected for losses during extraction Control samples taken through the pro cedure revealed that the inter and intra assay coefficient of variation was less than 15% Chromatographic separa tion of progesterone was not performed as the antiserum was shown to be highly specific for progesterone

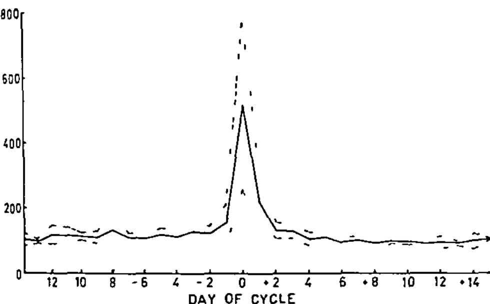
Assay of total estrogens

An aliquot of plasma was extracted with freshly distilled diethyl ether The total unconjugated estrogens in the extract were measured by a radioimmunoassay based on the method of Speroff and co-workers (10) although col umn chromatographic separation of the individual estro- gens was not performed The antiserum was used at a concentration of 1 18000 and approximately 20000 dpm 6 7-^{3}H-17β-estradiol (SA 56 Ci/mM The Radiochemical Centre) was added to the assay tube After a 18–24 h incubation at 0–4 C free and bound hormone were sepa rated by dextran coated charcoal The radioactivity in an aliquot of the supernatant (0 5 ml) was measured as de scribed in the assay of progesterone

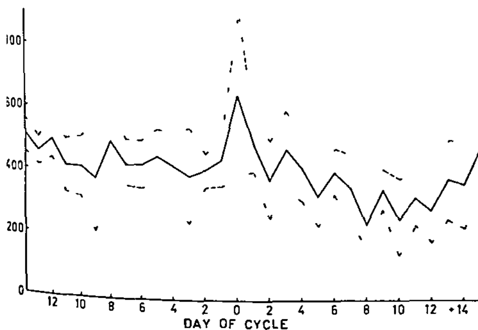
The antiserum reacts with estrone estradiol and estriol in the following ratios 100 30 3 respectively (10) The results were expressed as estradiol equivalents per ml of plasma

Fig 1 The mean and one standard deviation of plasma progesterone concentration during menstrual cycles in 14 Chinese subjects

Fig 2 The mean and one standard deviation of plasma total oestrogen concentration during menstrual cycles in 14 Chinese subjects



The mean and one standard deviation of plasma
zing hormone concentration during menstrual cy
14 Chinese subjects



4 The mean and one standard deviation of plasma
le stimulating hormone concentration during men
cycles in 14 Chinese subjects

Assay of luteinizing hormone (LH)

LH was estimated by a double antibody disequilibrium *radioimmunoassay similar to that described by Midgley* and others (5) using reagents supplied by the National Pituitary Agency National Institutes of Health Bethesda USA Iodination of high grade LH LER 960 (2 5 μg) was performed using $Na^{125}I$ by the method of Greenwood Hunter and Glover (3) Specific activities of approximately 100 $\mu Ci/\mu g$ were obtained Rabbit anti LH serum (Batch no 1) was used at a 1 8 000 dilution and this bound approximately 30% of added tracer The plasma sample (0 1 ml) was incubated at 0–4 C with the antibody for one day then the ^{125}I hormone was added and incubation continued for a further three days The second antibody (sheep anti rabbit gamma globulin) was added and incubated for another three days in the cold After centrifugation in the cold the supernatant was discarded and the precipitate counted in a Nuclear Chicago Gamma *Spectrometer The reference preparation employed was* LER 907 which has recently been assigned the following immunoreactivity 1 mg LER 907=60 IU of LH and 20 UI FSH 2nd IRP HMG

Assay of follicle stimulating hormone (FSH)

FSH was measured by a radioimmunoassay similar to that for LH The reagents were also supplied by the National Pituitary Agency National Institutes of Health Bethesda USA The rabbit anti FSH serum (Batch no 3) was used at a 1 4 000 dilution which was capable of binding approximately 20% of added tracer (^{125}I LER 1366 at specific activities of approximately 100 $\mu Ci/\mu g$)

RESULTS

All fourteen subjects menstruated regularly and had cycle lengths between 26 and 32 days (mean 29 2) The lengths of the follicular and luteal phases as etermined from the peak of LH activity were ,0±0 6 (range 12–20) and 14 2±0 3 (range 12–16) espectively

Using the mid cycle surge of LH as a reference *composite graphs of progesterone total estrogens* LH and FSH were constructed and are illustrated in Fig 1–4

Progesterone levels during the follicular phase were 0 63±0 10 ng/ml and the level began to rise on the day of the LH peak to a maximum of 17 9±4 2 ng/ml 6 days after the surge of LH

The concentration of estrogens was usually highest on the day preceeding the LH peak although in a few cases it coincided with the LH peak The peak level of total estrogen was 508 8 pg/ml A secondary peak was observed which paralleled the profile of progesterone having a peak 7 days after the LH surge of 364 4 pg/ml

The mean mid-cycle peak of LH was 512 7±132 3 ng LER 907/ml and the levels during the luteal phase were 98 7±12 0 ng LER 907/ml which is slightly lower than during the follicular phase (112 7±11 0 ng LER 907/ml) The pattern of FSH was not so well defined as LH but it d' ... on the same day as LH (662 1±81 7 ng LER 907/ml)

DISCUSSION

The hormone profiles observed during the present investigation were similar to those in Caucasian women (1 4 6 7 9 11 12) and Thai women (8)

Progesterone levels were similar to those reported in Caucasian women although lower than those reported in Thai women However the latter study used a different assay procedure (competitive protein binding) and the mean values were effected by the unusually high concentrations of progesterone measured in two of the six subjects studied

The concentrations of total estrogens are comparable to those in Caucasian and Thai women

The levels of LH during all phases of the menstrual cycle are slightly higher than those reported in Thai women (8) using the same standard preparation Other investigators have used different reference preparations and it is therefore difficult to give direct comparisons However calculations of data obtained in Caucasian women in terms of LER 907 *reveal similar levels to those reported in the present* study The LH concentration is slightly lower than that in the follicular phase due to the inhibitory feedback response of the steroids during the luteal phase

It is also difficult to make direct comparisons of our FSH data with similar data from other studies *due to the use of a variety* of standard preparations However the levels and certainly the profiles of *FSH* in plasma appear *to be similar* There was a much larger inter subject variation in the concentration of FSH compared with LH The concentration during the early follicular phase was high but did drop before the mid-cycle surge The steroids produced during the luteal phase caused a reduction of the FSH level in the blood by the feedback response on the hypothalamus but a rise of FSH was observed prior to menstruation

ACKNOWLEDGEMENT

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FSH Generous supplies of anti 11 hydroxy progesterone hemisuccinate BSA and anti 17β-estradiol hemisuccinate BSA sera were given by Dr K Kirton John Co Kalamazoo Michigan and Dr B V Cald Yale University School of Medicine New Haven Connecticut respectively We express our gratitude to Mr L Peh Miss A Chow and Miss H Mok for their valuable technical assistance We also thank the Wellcome Trust (UK) the China Medical Board and the World Health Organization for financial aid

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E COLI GROWTH INHIBITION BY AMNIOTIC FLUID

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tract Amniotic fluid samples were collected asepti y from ?9 normal pregnancies between the 38th and t week of gestation and checked for sterility in the la atory in order to investigate in vitro the effect of the or on the growth of E coli Brain Heart Infusion I I) and Ringer solution were used as controls E. coli ures were inoculated in amniotic fluid B H I Ringer ition and amniotic fluid plus B H I and incubated 7°C for 48 hours At 0 1 3 6 12 24 36 and 48 hours incubation, surface viable counts were performed to mate the number of E coli viable cells The growth of coli in B H I started during the 1st hour after inocula i and continued over 48 hours in Ringer solution the in growth curve was almost identical to that of B H I amniotic fluid the growth of E coli began from the 1st ir of inoculation but the growth curve was much lower ame static in ?4 hours and a permanent inhibition was erved thereafter The addition of a small amount of I I in amniotic fluid enhanced the growth of E coli the growth curve was lower in comparison to the ves of the two controls studied In conclusion after 48 irs of inoculation in amniotic fluid ?6 of the 29 cases ved bacteriostatic or bactericidal activity of the liquor on the growth of E coli

ntibacterial activity in amniotic fluid was reported the first time by Cattaneo (2) who suggested the sence of lysozyme while Gusdon (6) found a bstance bactericidal for Bacillus subtilis which l not appear to be lysozyme in approximately % of the amniotic fluids tested Contrary to the ove authors Walsh et al (11) and Sarkany & iylade (10) reported that human amniotic fluid es not exhibit antibacterial activity and generally ts as a good culture medium for bacteria More cently Galask & Snyder (4 5) have shown that nniotic fluid is inhibitory for a number of Gram sitive and Gram negative bacteria and have at mpted to identify the antibacterial factors in it milar results were reported by Bergman et al (1) who considered various antibacterial factors to ex ist in amniotic fluid acting alone or in combination

Inhibitory effects on the growth of E coli in amniotic fluid were reported by Galask & Snyder (4) Florman & Teubner (3) and Kitzmiller et al (7) which seemed to reflect the absence of nutrients in the liquor Furthermore Larsen et al (8 9) have demonstrated by measuring bacterial growth spectrophotometrically that amniotic fluid fails to support the growth of E coli but this inhibitory effect is lost when amniotic fluid i diluted in water or in a chemically defined medium (DDM)

The aim of the present study is to investigate the effect of amniotic fluid on the growth of F coli in order to determine any bacteriostatic or bactericidal activity of the fluid

MATERIAL AND METHODS

Amniotic fluid samples were collected aseptically during cesarean section or by abdominal amniocentesis from ?9 normal pregnancies between the 38th and 41st week of gestation All the above cases were uncomplicated preg nancies and had not received chemotherapy

Samples of amniotic fluid contaminated by blood or meconium were discarded from this study At the begin ning of the collection the first 10 ml of the liquor were discarded to avoid any mixture with traces of blood while the remainder was centrifuged at 3000 r p m for 15 min and the supernatant was kept in the deep freeze at −30°C The sediment was then checked for sterility

For this purpose the sediment was cultured (*a*) Aerobi cally on blood agar McConkey agar (BBL) M R S agar (Oxoid) and on Sabouraud maltose agar (BBL) (*b*) Anaerobically on blood agar and in thioglycollate broth (*c*) for Mycoplasmas on E Agar and in urea broth The supernatant was then used if it was sterile and free from blood or meconium

Testing of inhibitory activity Inhibitory activity of amniotic fluid was tested against Escherichia coli

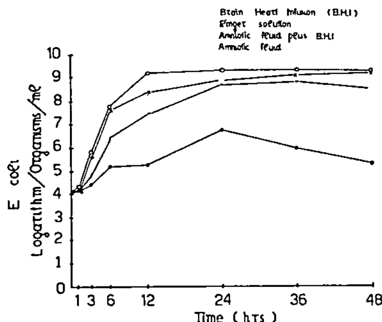


Fig 1 Growth curves of E coli in (a) amniotic fluid (b) amniotic fluid plus B H I (c) Brain Heart Infusion (control) and (d) Ringer solution (control)

N C T C 10418 Before use E coli was cultured on nutrient agar and incubated at 37°C for 18 hours Next day one loopful (by a 4 mm diameter wire loop) of E coli was inoculated in 5 ml Brain Heart Infusion (B H I) and incubated at 37°C for another 18 hours After incubation the broth-culture was diluted to 1 10^{-4} in B H I From this final dilution (containing 105×10^2 organisms per ml) 0 1 ml was added to each of the following media

1 To 2 ml of amniotic fluid
2 To 2 ml of amniotic fluid enriched by B H I 10%
3 To 2 ml of B H I
4 To 2 ml of Ringer solution

The last 2 tubes were controls No 3 checking E coli growth in a favourable medium without inhibitors and No showing E coli viability in the absence of any organic tnent Both amniotic fluids and controls were incubated at 37°C for 48 hours At 0 1 3 6 12 24 36 and 48 hours of incubation surface viable counts were performed for estimating the number of E coli viable cells (Miles & Mizra s method 1938) Ringer solution was used as diluent and dilutions were made up to 1 10^{-8}

RESULTS

The growth curves of E coli in Brain Heart Infusion (B H I) Ringer solution amniotic fluid plus B H I and amniotic fluid neat over 48 hours measured at 1 3 6 12 24 36 and 48 hours by plate counting are shown in Fig 1

The mean values of viable counts are given in 29 experiments for amniotic fluid in 15 for B H I in 15 for Ringer solution and in 14 experiments for amniotic fluid plus B H I The growth of E coli in B H I started during the first hour after inoculation and was continued over 48 hours in Ringer solution the mean growth curve was almost identical to that of the other control (B H I)

In amniotic fluid the growth of E coli began from the 1st hour of inoculation but the growth rate was much lower became static in 24 hours and permanent inhibition was observed thereafter Finally the addition of a small amount of B H I to the amniotic fluid enhanced the growth of E coli but the growth curve was lower in comparison to the curves of the two controls studied

Furthermore the individual growth rates of E coli cells in amniotic fluid (29 cases) are ... in Table I As it is shown from this table bacteriostatic activity of amniotic fluid on growth of E coli was observed in two of the cases at 6 hours six at 12 hours six at 24 h... eight at 36 hours and seven at 48 hours respect...

Bactericidal activity of the fluid occurred at ... hours in seven cases at 36 hours in thirteen cases and at 48 hours in nineteen cases

In conclusion after 48 hours of incubation ... the 29 cases showed a bacteriostatic or bacter... activity of the amniotic fluid on the growth of E coli

DISCUSSION

Walsh et al (11) and Sarkany & Gaylarde ... reported that the total viable counts of E Coli ... 24 hours of incubation in amniotic fluid were ...

e I *Individual growth rates of living E coli cells inoculated in amniotic fluid (1ml) for 48 hours*
acteriostatic activity * bactericidal activity

of	Hours of inoculation							
	0	1	3	6	12	24	36	48
	112×10^2	208×10^2	$1\,600\times10^2$	$5\,200\times10^2$	$4\,000\times10^2$	640×10^2	120×10^2	8×10^2▲
	136×10^2	188×10^2	600×10^2	$1\,400\times10^2$	$1\,520\times10^2$	560×10^2	160×10^2	100×10^2▲
	132×10^2	240×10^2	840×10^2	$3\,200\times10^2$	$2\,400\times10^2$	240×10^2	0	0
	152×10^2	228×10^2	520×10^2	$1\,280\times10^2$	480×10^2	0	0	0
	136×10^2	140×10^2	400×10^2	$1\,280\times10^2$	$3\,600\times10^2$	$7\,200\times10^2$	120×10^2▲	0
	28×10^2	32×10^2	160×10^2	112×10^2	56×10^2	0	0	0
	20×10^2	20×10^2	30×10^2	72×10^2	42×10^2	0	0*	0
	42×10^2	68×10^2	160×10^2	440×10^2	$4\,000\times10^2$	$640\,000\times10^2$	$184\,000\times10^2$	160×10^2
	24×10^2	32×10^2	88×10^2	200×10^2	400×10^2	40×10^2	20×10^2▲	0
	128×10^2	152×10^2	840×10^2	$6\,800\times10^2$	$3\,600\times10^2$	$1\,040\times10^2$	80×10^2▲	0
	$1\ 4\times10^2$	180×10^2	720×10^2	$3\,200\times10^2$	600×10^2	40×10^2▲	0	0
	140×10^2	156×10^2	144×10^2	$1\,120\times10^2$	520×10^2	40×10^2▲	0	0*
	116×10^2	200×10^2	960×10^2	$2\,800\times10^2$	$4\,000\times10^2$	$680\,000\times10^2$	$2\,400\times10^2$	72×10^2▲
	100×10^2	140×10^2	280×10^2	600×10^2	480×10^2	88×10^2▲	0	0
	140×10^2	180×10^2	180×10^2	140×10^2▲	100×10^2▲	0	0*	0
	92×10^2	120×10^2	240×10^2	$1\,600\times10^2$	$2\,800\times10^2$	640×10^2	$1\ 0\times10^2$	40×10^2▲
	140×10^2	160×10^2	420×10^2	$1\,400\times10^2$	$1\,600\times10^2$	800×10^2	400×10^2	80×10^2▲
	100×10^2	120×10^2	600×10^2	$2\,080\times10^2$	$4\,000\times10^2$	$5\,600\times10^2$	$1\,200\times10^2$	520×10^2
	152×10^2	240×10^2	320×10^2	960×10^2	600×10^2	0	0	0
	116×10^2	140×10^2	520×10^2	$3\,200\times10^2$	$1\,100\times10^2$	400×10^2	80×10^2▲	0
	48×10^2	60×10^2	60×10^2	80×10^2	40×10^2▲	40×10^2▲	▁0×10^2▲	0
	92×10^2	100×10^2	160×10^2	120×10^2	80×10^2▲	20×10^2▲	0	0
	$4\ \times10^2$	54×10^2	92×10^2	240×10^2	$2\,400\times10^2$	$80\,000\times10^2$	$120\,000\times10^2$	$64\,000\times10^2$
	132×10^2	180×10^2	400×10^2	800×10^2	$3\,600\times10^2$	$1\,040\times10^2$	100×10^2▲	40×10^2▲
	136×10^2	140×10^2	180×10^2	160×10^2	100×10^2▲	36×10^2▲	0	0
	128×10^2	160×10^2	400×10^2	180×10^2	120×10^2▲	0	0*	0*
	112×10^2	152×10^2	840×10^2	$4\,000\times10^2$	$3\,600\times10^2$	800×10^2	42×10^2▲	10×10^2▲
	140×10^2	192×10^2	640×10^2	$2\,000\times10^2$	$1\,100\times10^2$	600×10^2	100×10^2▲	0
	92×10^2	120×10^2	120×10^2	80×10^2▲	10×10^2	0	0	(

those in Trypticase soy broth Contrary to the findings Galask & Snyder (4) showed inhibi f E coli growth by amniotic fluid but the rate wth was measured by recording turbidometric es (spectrophotometrically) of the inoculated amples Furthermore Bergman et al (1) pre l an inhibitory activity of the amniotic fluid it E coli in 66 6% of the samples tested La itzmiller et al (7) using direct viable counts a lack of E Coli growth in clear amniotic while the addition of 0 5 ml of trypticase soy supported a normal rate of growth with a growth curve nearly identical to that in the trypticase soy broth

the present investigation direct viable counts ve dilution and plate counting methods performed Clear amniotic fluid B H I solution and amniotic fluid plus B H I used as media for the growth of E coli

results obtained revealed a much lower curve of E coli in clear amniotic fluid which became static in 24 hours in all cases while afterwards a permanent inhibition was noticed (bacteriostatic activity) until 48 hours when in 19 samples a bactericidal effect was observed

In B H I and Ringer solution which were used as controls the mean growth curves of E coli were nearly identical Besides the addition of a small amount of B H I to the amniotic fluid enhanced the growth of E coli in it but the curve was lower in comparison with the two controls

The results of this series agree partly with those of Kitzmiller (7) who suggested that growth inhibition of E coli by amniotic fluid is due to the absence of nutrients The main difference between the results of the present study and those of other authors is that the inhibitory effect of the amniotic fluid started in a few cases after six hours of inoculation and continued in such a rate that after 48 hours 26 of the 29 samples presented a high degree of inhibition with predominance of a bactericidal effect (19 samples)

The presented data support the view that there is a permanent antibacterial activity in amniotic fluid upon E coli growth in vitro which perhaps exists in a similar way *in vivo* thus protecting both mother and fetus from infection especially after bacterial invasion into the amniotic cavity during pregnancy and labor

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EFFECT OF A COPPER AND A PLASTIC IUD ON THE HISTOCHEMISTRY OF ENDOMETRIAL ENZYMES IN THE RABBIT DURING EARLY PSEUDOPREGNANCY

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ct The influence of a copper and a plastic IUD on calization and intensity of alkaline and acid natase and beta-glucuronidase activity in the rabbit etrium during early pseudopregnancy was investi- The activities of the two lysosomal enzymes acid natase and beta-glucuronidase were increased in e epithelial cells in the presence of both types of The alkaline phosphatase activity was almost etely abolished in surface and glandular epithelial n uterine horns

ous types of inert IUDs have been found to ere with the activity of endometrial enzymes he presence of inert IUDs *alkaline phatase* activity in human endometria was ted to be normal (14 27) or increased (16 18) creased activity of alkaline phosphatase was d in wearers of the Cu T (13)

a study of homogenates of the rat uterus the ity of alkaline phosphatase was increased in resence of surgical silk or a copper IUD (5 6) e non pregnant rabbit it was unaltered in the ence of "inert IUDs (19 21)

e acid phosphatase activity was found to be ased in the presence of inert" and copper in the human (13 18 20) Hester et al (16) did find the normal increase in this enzyme s ity at the time of ovulation in the presence of inert IUD

n increased activity of acid phosphatase was found in the rat in the presence of inert and IUDs (5 6 17 20) and in the rabbit in the a copper IUD (?) but not of an inert ?1)

In wearers of the Cu T the activity of beta glucuronidase was somewhat depressed (13) whereas it was reported to be increased in the rat in the presence of both surgical silk and copper (5 6) Six of the above cited studies are histochemical (- 14 16 19 21 and 27)

In our previous studies the DNA synthesis and the morphological development of the endometrium (9 10 11) were markedly inhibited in the presence of a copper IUD during early pseudopregnancy and early pregnancy in the rabbit As it has been suggested that alkaline phosphatase acid phosphatase and beta glucuronidase are of importance for the implantation process in this animal (1 8 12 24) the effect of a plastic and a copper IUD on the activity of these enzymes was studied in the same experimental system

MATERIAL AND METHODS

Virgin rabbits of mixed breed weighing 2–3 kg were used Two types of IUDs were studied 1) Copper IUD—consisting of a 50 mm long polyethylene catheter 0 5 mm in outer diameter (Clay Adams Parsippany N Y USA) around which a copper wire 0 23 mm in diameter was coiled giving a surface area of 200 mm² (*Cu IUD*) ?) Plastic IUD—consisting of a polyethylene catheter 1 0 mm in outer diameter and 50 mm long (*Pl IUD*$_{1.0}$)

The IUDs were sterilized by soaking in ethanol and rinsed in sterile physiological saline before use The animals were anaesthetized with Nembutal and the abdominal cavity was exposed under sterile conditions via a lower abdominal midline incision No corpora lutea were present at the time of operation The IUDs were introduced into the uterine horns via a small puncture in the antimesometric part of the uterine wall and fixed by a

Table I *Presentation of various experimental groups with number of animals and main effects of d types of IUDs*

Group	Combinations of IUDs	Subgroups (hours)	No of animals	Main effects of Pl $IUD_{1,0}$ and Cu IUD on the activi calization of alkaline phosphatase acid phosphatase a glucuronidase
I	Pl $IUD_{1,0}$-SH	0 120	6 6	*Alkaline phosphatase* In Pl $IUD_{1,0}$ exposed horns at 0 hours essentially the same appearance a for s horns (see text) *Acid phosphatase* In Pl $IUD_{1,0}$ exposed horns at 0 crease in the activity of the enzyme in the apical surface epithelium At 120 hours no difference fro operated horns *Beta glucuronidase* In Pl $IUD_{1,0}$ exposed horns at 0 more intense staining in the surface epithelial cells epithelially intensely stained inflammatory cells At 1 no difference from sham-operated horns
II	Pl $IUD_{1,0}$-Cu IUD	0 120	6 6	*Alkaline phosphatase* In Pl $IUD_{1,0}$ exposed horns at 0 hours see above for Group I In Cu-IUD horns at 0 and 120 hours an almost completely abol tivity in surface and glandular epithelial cells As a number of inflammatory cells with an intense enzyme *Acid phosphatase* In Pl $IUD_{1,0}$ exposed horns at 0 and 1 see above for Group I In Cu IUD exposed horns at no difference from Pl $IUD_{1,0}$ horns At 1 0 hours an i enzyme activity in areas of the surface epithelial cells c with Pl $IUD_{1,0}$ horns *Beta glucuronidase* In Pl $IUD_{1,0}$ exposed horns at 0 hours see above for Group I In Cu IUD exposed h hours no difference from Pl $IUD_{1,0}$ horns At 120 hou creased activity in surface epithelial cells especially at the minor folds Strong enzyme activity in inflammatory

4-0 silk suture at the site of the puncture Uterine horns designated as sham-operated (SH) were exposed to introduction and withdrawal of the Pl $IUD_{1,0}$ 4-0 silk suture being placed at the site of the puncture The effect of the Cu IUD was compared with that of the Pl $IUD_{1,0}$) in the same animal One horn was fitted with the Pl $IUD_{1,0}$ and the other with the Cu IUD except in the group where one of the horns was sham-operated The IUDs were always randomized between the horns

On the fifth day after operation most of the animals were injected with HCG—75 IU (HCG human chorionic gonadotropin Gonadex Leo AB Helsingborg Sweden) intravenously to induce pseudopregnancy Some animals killed on the fifth day after operation were not injected with HCG (0 hours) Table I lists the experimental groups The animals were killed by cervical dislocation at 0 and 120 hours after injection The internal genitalia were taken out and the uterine horns were trimmed The presence of corpora lutea in each ovary was registered The middle part of the length of the uterine horn exposed to the IUDs was used for enzyme studies

The tissue was immediately frozen in propane cooled by liquid nitrogen and preserved at −70°C until further processed Cryostat sections were fixed either in 10% formalin (containing 0 07 M phosphate buffer pH 7 4) for 10 min or in absolute acetone at −20°C for 15 min and for another 15 min at room temperature The forma sections were rinsed for 5 min in 0 1 M phospha (pH 7 4)

The acetone fixed sections were stained phosphatase and beta glucuronidase The reactio carried out according to azo-dye methods with AS TR phosphoric acid (sodium salt) as substra two phosphatases (3 4) and naphtol AS BI-glu for the beta glucuronidase (15) The tissue secti incubated for 30 min for the alkaline phosphatase (pH 9 1) and for 60 min for the acid phosphatase and beta glucuronidase reaction (pH 5 2) The procedures were checked with simultaneous inc of rat liver sections which showed a normal pattern

RESULTS

Alkaline phosphatase activity

The normal development of the endometriu HCG injection was essentially the same scribed previously (11) to judge from section sham-operated horns stained for alkaline phatase and studied at 0 and 120 hours





The alkaline phosphatase activity in the apical part surface epithelial cells of a Pl IUD$_{1,0}$-containing (a) is almost completely abolished in the Cu IUD-containing horn (*b*) The comparison is mad between horns within the same animal

e alkaline phosphatase activity in the en trium of unstimulated (0 hours) sham ted horns (in animals where the other horn fitted with the Pl IUD$_{1,0}$) was localized as a granular line in the apical part of most of the ce and glandular epithelial cells There was an intense activity just beneath the epithelium n the endothelial lining of the stromal vessels ctivity was found in the stromal cells

1?0 hours after HCG stimulation the alka hosphatase activity was markedly increased ly localized in the apical part of the surface elial cells In addition an intense activity in thin stromal septa of the minor folds was rved (Fig 1 A) The activity of the glandular ial cells was generally faint in some areas ty could be found In the subepithelial of the glands the activity was generally The activity of the endothelial cells of l vessels had the same appearance as that d in unstimulated rabbits

rance of the alkaline phosphatase ac in the presence of the Pl IUD$_{1,0}$ was essentially the same as that described above for sham operated horns irrespective of the treatment of the contralateral horn sham-operation or exposure to the Cu IUD

In horns fitted with the Cu IUD the alkaline phosphatase activity was almost completely abolished in surface and glandular epithelial cells at 0 and 120 hours (Fig 1 B) Furthermore there was a markedly increased number of inflammatory cells with an intense alkaline phosphatase activity These cells were found subepithelially and in the uterine lumen

Effect of cupric ions on the alkaline phosphatase reaction

As the alkaline phosphatase activity was almost completely abolished in endometrial cells exposed to the Cu IUD sections from sham-operated horns (120 hours after HCG injection) were stained for alkaline phosphatase in the presence of cupric ions (cupric acetate–*pro analysi* added to give final cupric ion concentrations from 3×10^{-4} to

3×10^{-2}M) Cupric ions at these concentrations were found to reduce the alkaline phosphatase staining during the first 15 min of incubation However the intensity of staining after 30 min of incubation was the same as in control sections where no cupric ions were added to the reaction mixture

Acid phosphatase activity

A faint and mainly granular acid phosphatase activity was seen in the apical part of the surface and glandular epithelial cells in sham operated horns at 0 hours Faint acid phosphatase activity was also found in the endothelium of stromal vessels and in scattered stromal cells

At 120 hours no activity could be found in most surface epithelial cells The glands showed essentially the same activity as described above at 0 hours The endothelial cells in the stromal vessels and scattered stromal cells showed a faint enzyme activity There was a tendency to an accumulation of the stromal staining beneath the surface epithelium

The endometrium of horns fitted with the Pl $IUD_{1,0}$ showed the same localization and intensity of acid phosphatase activity as sham-operated horns except at 0 hours when the activity of the apical part of the surface epithelium was increased The Pl $IUD_{1,0}$ had no obvious effect on the staining of the glandular epithelial cells The same picture was obtained in the presence of the Pl $IUD_{1,0}$ irrespective of the type of treatment of the contralateral horn—sham-operation or exposure to the Cu IUD

No difference in the acid phosphatase activity could be found in the endometrium of horns fitted with the Cu IUD or the Pl $IUD_{1,0}$ in unstimulated animals At 120 hours areas of more intense enzyme activity mainly localized in the surface epithelium were found in horns exposed to the Cu IUD

Beta glucuronidase activity

In sham-operated horns at 0 hours enzyme activity was seen in the surface and glandular epithelial cells with a more pronounced activity in the apical part of the cells Activity was also found in inflammatory cells lying in the stroma

At 120 hours the activity of this enzyme was generally weaker being mainly localized in the basal part of the surface epithelial cells a[illegible] apical part of the glandular epithelial cells

At 0 hours horns fitted with the Pl-I[illegible] showed a more intense staining in the apical [illegible] the surface epithelial cells Furthermore [illegible] creased number of stained (probably inflammatory) cells lay in the stroma At 120 hours there was [illegible] definite difference between Pl $IUD_{1,0}$-contain[illegible] horns and sham-operated horns

The appearance of the beta glucuronidase [illegible] ity in horns fitted with the Cu IUD studied at [illegible] hours was the same as described above for [illegible] containing the Pl $IUD_{1,0}$ At 120 hours the [illegible] epithelial cells of the Cu IUD-containing [illegible] showed an increased enzyme activity especi[illegible] areas at the top of the minor folds There were [illegible] stained inflammatory cells in the stroma, [illegible] accumulated beneath the surface epithelium [illegible]

DISCUSSION

The appearance of the enzyme activity (alk[illegible] and acid phosphatase and beta glucuronidase [illegible] sham operated horns of pseudopregnant [illegible] studied in the present investigation agrees [illegible] with that described by Petry et al (24) for [illegible] horns

Different kinds of IUDs have been found [illegible] interfere with the activities of several endom[illegible] enzymes among these the most frequently [illegible] are alkaline phosphatase acid phosphatase [illegible] beta glucuronidase These enzymes are of spe[illegible] interest they are supposed to participate in [illegible] implantation process (1 8 12 24) Further[illegible] acid phosphatase and beta glucuronidase [illegible] lysosomal enzymes and copper is known to [illegible] cumulate in the lysosomes (2) therefore the [illegible] of these enzymes might be altered in the prese[illegible] a copper IUD and possibly also in the presen[illegible] inert IUDs as these have been found to cause [illegible] increase in the copper concentration in the [illegible] fluid of women (26)

Alkaline phosphatase activity in human [illegible] dometrial surface epithelial cells increases as [illegible] endometrium grows and reaches a peak d[illegible] late proliferative stage (22) This enzyme [illegible] the presence of zinc for optimum activity [illegible] as discussed by Zipper (29) might there[illegible] affected by the presence of other cations [illegible] cupric ions

ert" IUDs have generally been found to in e the acid phosphatase activity both in rats (5 20) and in women (18) In rabbits the activity is enzyme was reported to be unaltered (21) slightly increased epithelial activity in the nce of the Pl $IUD_{1.0}$ described in the present r is at variance with the latter finding

pper IUDs were reported to cause an in ed activity of acid phosphatase in various ies (? 6 13) Similar results were obtained in resent study

the present investigation the epithelial activity ta-glucuronidase was increased and a greater ber of positive inflammatory cells appeared in resence of both types of IUDs—especially in of the Cu IUD In homogenates a greater ity was reported from studies in the rat (5 6) ever in women wearing the Cu T the activity us enzyme was found to be slightly decreased As polymorphonuclear leucocytes are rich in -glucuronidase the different results might be to differences in the number of inflammatory (cf 7 13)

the rat both a copper and an inert IUD lted in a higher uterine alkaline phosphatase ity (5 6) This activity was found to be tered (14 19 21 27) or increased (16 18) in the ence of inert IUDs in different species The T in women caused a decreased activity (13) results agree well with the latter finding as the line phosphatase activity of epithelial cells was st completely abolished in the presence of a er IUD The present study found that a plastic had no influence on the activity of alkaline sphatase Again some of the differences in the lts of various reports might be explained by the ision of leu ocyte alkaline phosphatase activity ochemical determinations

ison (28) has demonstrated a reduced activity human endometrial alkaline phosphatase in ogenates both in the presence of a copper foil cupric ions This agrees with our finding that alkaline phosphatase staining during the first 15 of incubation was reduced in the presence of ric ions However after 30 min of incubation alkaline phosphatase staining in the presence of ric ions was identical with that in control ions The alkaline phosphatase staining is thus bited by cupricions but probably not enough to lain the complete loss of activity in the surface helial cells of horns exposed to the copper IUD *in vivo* Thus there might be a lack of this enzyme in the epithelium which can be due to a differentiation defect

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PROGNOSIS RECURRENCES AND METASTASES CORRELATED TO HISTOLOGIC CELL TYPE IN CARCINOMA OF THE UTERINE CERVIX

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ract An analysis of 230 patients treated with radio- apy for cervical cancer stages I and II is presented No ive correlation to cell type was found as regards the ber of failures recurrence rate or the frequency of nal or distant metastases Although different biologi ehavior might be shown by cancers of varying cell s adequate planning and staging before treatment ms to be of better prognostic value

cer of uterine cervix is in its early stages essfully treated both by surgery and/or radio- apy Several attempts have been made to select tment according to the cytologic and histo iologic classification made upon smears or psies from the tumour (2 6) Varying results e be n obtained but so far no consistent guide s as regards the future treatment of the patient be based on the morphologic picture This ms to be relevant in addition to squamous cell cer of the uterine cervix when subclassified ac ding to criteria presented by Reagan et al 1957)

Thus some investigators have found that patients h squamous cell cancer of small cell type as well patients with keratinizing squamous cell cancer e less chance of survival when compared with a up of patients having squamous cell cancer of non keratinizing type when all were treated by iotherapy (16 22) However others were not e to demonstrate any difference in survival or the qu n y of recurrences among patients treated by iotherapy stating that surgery for stages I and II uamous cell carcinoma of the cervix will have to justified on a basis other than tumour grade (7)

The present investigation correlates death from cervical cancer and number of recurrences and metastases to regional lymph nodes and distant or gans with the three groups of histopathologic cell differentiation as suggested by Reagan et al 1957 (18)

MATERIAL AND METHODS

Case material is comprised of 230 women with stages I and II carcinoma of the uterine cervix according to FIGO 1970 (24) that were treated during 1969 and 970 in the Gynecologic Section Department of Radia ion Therapy University Hospital Lund Sweden

Patients were treated according to the following princi ples External high voltage irradiation later supplemented by intracavitary treatments was given to most of the pa tients Exceptions were made in patients with small and early tumors they being given only intracavitary treat ment in two sessions 3 weeks apart When combined ex ternal and intracavitary treatment was chosen only one application was given The interval between external and intracavitary treatment was three weeks

External irradiation was given with ^{60}Co and 33 MV photons dependent upon the size and configuration of the patient The pelvis was given 850–950 rad each week in five fractions using two opposing fields The field size was determined from the size of the pelvis Both fields were treated daily

Point A (2 cm lateral and 2 cm cranial from the external os of the uterine cervix) is the reference point for given absorbed dose The external treatment was supposed to deliver a dose between 3 000–4 500 rad at point A

Ea h intracavitary treatment lasted 12–20 hours At point A the dose rate was 150–200 rad/h according to type of applicators used These have been described previ ously (10) They can be locked in a definite position which implies that the dose measured in point A is rep- resentative for the whole treatment

76263

Table I *Distribution of 230 patients with uterine cervical cancer according to cell type and stage 1969–1970*

Cell type	Stage 1	Stage 2	Total no
Non keratinizing ca	10?	68	170 (74%)
Keratinizing ca	13	22	35 (15%)
Small cell ca	0	6	6 (3%)
Adeno-squamous ca	1	4	5 (2%)
Adenocarcinoma	7	7	14 (6%)
Total	123	107	230 (100%)

The total dose at point A from external and intra cavitary irradiation varied between 5000–7000 rad dependent on the size and extension of the tumor and the dose estimated to be received by the urinary bladder and rectum When calculating the external and intracavitary dose no correction has been made for the difference in biologic effects due to different fractionation scheme (4) Patients having an adenocarcinoma were given 3000–4500 rad to the pelvis as described above and six weeks after radiotherapy a total hysterectomy including a vaginal cuff was performed (9) According to the findings at operation supplementary radiotherapy was given afterwards

In a few cases the anatomy of vagina and cervix did not permit the use of the radium applicators as described above Then supplementary external treatment up to 6500 rad was given to the primary tumor about –3 weeks after the initial series of treatment (21 patients) Occasionally intracavitary applicators were used which do not permit adequate dose estimation (5 patients)

The histopathologic classification relies on biopsy specimens small for diagnostic purposes and cone biopsies made in an attempt to excise the tumor In pa[illegible] with an adenocarcinoma there is a post therapeutic [illegible]sterectomy specimen which also is available in many [illegible]nts with recurrences of the squamous cell variety

Five different groups were used squamous cell cancer of small cell type of keratinizing large cell type of non keratinizing large cell type pure adenocarcinoma and adeno squamous cancer In specimens with transitional forms or of mixed types the dominant pattern has decided

Table II *Death from cancer of 230 patients with uterine cervical cancer according to cell type and stage during an observation period of 3 5–5 5 years*

Cell type	Stage 1	Stage 2	Total no
Non keratinizing ca	4/10?	16/68	20/170 (12%)
Keratinizing ca	3/13	5/??	8/35 (~23%)
Small cell ca	0	3/6	3/6
Adeno-squamous ca	0/1	2/4	?/5
Adenocarcinoma	0/7	4/7	4/14
Total	7/123 (6%)	30/107 (28%)	37/230 (16%)

Table III *Frequency of recurrences in 2?? pa[illegible] with uterine cervical cancer in relatio[illegible] to cell [illegible] and stage during an observation period of 3 5[illegible] years*

Cell type	Stage 1	Stage ?	Total no
Non keratinizing ca	3/102	9/68	1?/170
Keratinizing ca	?/13	4/22	6/35 ([illegible]
Small cell ca	0	?/6	2/6
Adeno-squamous ca	0/1	3/4	3/5
Adenocarcinoma	0/7	?/7	2/14
Total	5/123 (4%)	20/107 (19%)	25/230 (11%)

the classification but a clarifying notation is added [illegible] the statistical results are evaluated

All patients have been observed between 3.5-5 5 [illegible] The diagnosis of recurrences and/or metastases was [illegible] by physical and radiologic examination [illegible] biopsies The patients have not been [illegible] progression of residual tumor or recurrences (5) [illegible] recurrent tumor growth or metastases were detected [illegible] therapy was finished *only the first site* has been [illegible]

RESULTS

In Table I the histopathological diagnoses are [illegible] with all patients grouped in stage I or stage II [illegible] significantly lower number of large cell [illegible] keratinizing cancers was found in stage II in [illegible]parison with stage I ($p < 0.05$)

The proportion of patients who died from [illegible] disease is somewhat higher among women [illegible] large cell keratinizing cancer as compared to [illegible] with large cell non keratinizing squamous [illegible] cancer The difference however is not statis[illegible] significant and is only observed in stage I p[illegible]

Table IV *Frequency of lymph node metastas[illegible] 230 patients with uterine cervical cancer in rel[illegible] to cell type and stage during an observati[illegible] of 3 5–5 5 years*

Cell type	Stage 1	Stage ?	Total [illegible]
Non keratinizing ca	?/10?	3/68	[illegible]
Keratinizing ca	0/13	0/	[illegible]
Small cell ca	0 0	0 6	[illegible]
Adeno-squamous ca	0/1	0/4	[illegible]
Adenocarcinoma	0/7	1/7	[illegible]
Total	2/123 ([illegible])	4/107 (4%)	[illegible]

e V *Frequency of distant metastases in 230 nts with uterine cervical cancer in relation to type and stage during an observation period of 5.5 years*

type	Stage 1	Stage 2	Total no
-keratinizing ca	0/102	6/68	6/170 (4%)
tinizing ca	1/13	0/22	1/35 (~3%)
l cell ca	0/0	2/6	?/6
no-squamous ca	0/1	0/4	0/5
nocarcinoma	0/7	1/7	1/14
l	1/123 (1%)	9/107 (8%)	10/230 (4%)

number of patients in these particular groups is low to permit a conclusive statistical evaluation ble II) Among stage I patients with large cell itinizing cancer one did not receive adequate acavitary treatment which resulted in a local irrence that was not possible to cure One pa t with fatal large cell non keratinizing cancer given external radiotherapy only In Tables III and V are given the frequency of recurrences number of patients with metastases to regional ph nodes and to distant organs are tabulated significant differences can be found statistically the number of positive observations in each up is too low to permit statistical evaluation re is a tendency to a lower frequency of urrence and a higher percentage number of tastases to regional lymph nodes among women h large cell nonkeratinizing squamous cell car oma Among the 25 patients with recurrences were seen in the group of non keratinizing large l carcinoma Seven out of these twelve patients re found to have a poorly differentiated squa us cell cancer with large occasionally bizarre iamous cells demonstrating a total absence of atinization These cancers do not fulfil the cri ia of a small cell carcinoma but using common tologic criteria must be regarded as poorly dif entiated carcinomas (1)

DISCUSSION

r a long time treatment of early stages of invasive rcinoma of the uterine cervix has been a contro- rsial matter Some advocate a surgical procedure the most effective (17) while others favor radio- era y as the initial choice The results in these nes seem to be equally good and comparable both in regards to cure rate and complication rate (3 12 14 15 19 21)

Several attempts have been made to correlate histologic cell type with the prognosis of the patient with a uterine cervical carcinoma Some authors were not able to find such a correlation (13) while other results (23) indicate a favorable prognosis in patients with non keratinizing squamous cell cancer in comparison with cancer of other cell types However it is not satisfactory to rely on the cure rate only when the efficiency of a particular treat ment is to be evaluated All separate factors in fluencing the prognosis have to be considered Among these the initial treatment of the primary tumor has to be studied in particular but in addi tion local spread of the tumor as well as metastases to regional lymph nodes are of interest as these areas can be effectively treated with various tech niques For distant metastases no curative treat ment can be offered at present

Most series are presented in an attempt to corre late the histopathology to the survival rate The results so far have been controversial (7 16 22 23)

Attempts have been made to correlate the histo- pathologic picture to both local failures and all other treatment failures (7) No statistically conclusive evidence has been obtained mainly due to the low number of such failures

An attempt to evaluate the prognostic value of the histopathological classification is not possible unless the patients have well-defined tumors which display a limited spread viz stage I or II In addi tion a biopsy from more advanced tumors is less likely to be representative The more advanced tumor in addition generally offers greater thera peutic problems and an estimation of the delivered dose might be more difficult to calculate due to patient and tumor-dependent variables in each case

The technique applied is of decisive importance in order to obtain favorable results in a given pa tient Some previously reported failures might be explained by inadequate radiotherapy (7) How ever the use of modern radiotherapy with intra cavitary applicators does not imply that the esti mated dose can be used as an indicator of radio- sensitivity or even radiocurability Several dif ficulties are apparent when the dose given to the tumor area is calcula ed even if locked or combined applicatos are used (10 20) When separate intra uterine and intravaginal applicators are preferred

this estimation is practically impossible The use of point A as representative for absorbed dose is possible only if the distribution of radiation around each applicator combination is known in detail In the present series of patients the dose at point A varied between 5000–7000 rad while the absorbed dose in the central part of the uterine cervix was estimated to vary between 9000–16000 rad When external radiotherapy is given alone however a well defined and even dose is applied to the tumor area

In 21 patients in this series receiving external therapy solely the absorbed dose is considered to lie within ±10% of the calculated dose This has been confirmed by dose measurements *in vivo* that are routinely made in all patients (11) Among these 21 patients 17 had squamous cell cancer Of these 12 were of large cell non keratinizing type and in this group 3 recurrences were observed The remaining five patients were of large cell keratinizing type and here no recurrences were observed

The statistical analysis could not reveal a positive correlation between histological cell type and recurrence rate number of failures of radiotherapy and frequency of metastases to regional lymph nodes or distant organs Although the number of patients in each group is small which makes a statistical analysis less reliable or even impossible the results obtained may be explained in at least two different ways

1 There is no apparent difference in biological ehavior between cancer of different cell types is explanation seems less plausible as a number of observations indicate several points of difference in behavior (1 16 18)

2 The radiotherapy administered as described above is equally effective for all types of cancers A failure is not dependent on cell type and biological behavior but on inadequate staging before treatment or factors persistent in a given patient such as abnormal anatomical conditions and/or inadequate positioning of intracavitary applicators—factors obviating an optimal treatment

CONCLUSION

This investigation has not been able to demonstrate significant prognostic differences allowing statistical analysis between the two histopathological types of squamous cell cancers (large cell keratinizing and large cell non keratinizing squamous cell cancer) Thus a pretreatment classification of histologic subgroups has been of limited value as regards planning the treatment of the patient In order to improve the results an analysis in detail of all technical aspects of the treatment as well as accurate preliminary staging seems to be more beneficial (8)

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VALUE OF ULTRASONIC DIAGNOSIS OF GYNECOLOGICAL TUMORS IN 370 SURGICAL CASES

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tract Ultrasonic exploration of the female pelvis to firm or supplement the usual clinical examination ena d a correct diagnosis to be made in 80% of the 370 es examined and subsequently operated on The ographic description always included the size of the tor its cystic or solid nature and its site of origin Out 3 uterine and ovarian tumors measuring less than 3 cm y 15 were discovered

lvic tumors were revealed by means of rasound as early as 1958 by Donald (2) since n the two-dimensional echographic aspects of necological tumors have been described fre ently (3–14) The value of echographic diagnosis pelvic masses in gynecology was assessed from a ies of 69 patients by Levi in 1971 (9) That study s been pursued further and the cases of 370 wo n operated on after ultrasonic examination are ported in this paper The ultrasonic technique and r method used to interpret the echograms were blished earlier (9–10)

MATERIAL AND METHOD

om 1968 to March 1974 8 112 patients were examined at Ultrasound Diagnosis Department of the Clinic for stetrics and Gynecology Hôpital Universitaire ugmann Brussels 519 examinations had been re ested to confirm or complement the clinical diagnosis f these 519 patients 370 later underwent surgery the bseque t m croscopic and microscopic description of e genital organs was then compared with the pre erative echographic description in order to check the trasonic diagnosis

The report on the echogram contains details which rmit (1) detecting the presence or absence of a pelvic ass (2) defining its nature solid cystic or complex umor with solid tissues and liquid areas) (3) measuring e tumors and (4) pinpointing heir origin as closely as ssible (uterus ovaries Fallopian tubes etc)

The macroscopic and microscopic diagnoses erved as a reference or final diagnosis The ultrasonic diagnosis (USD) was classified as

(*a*) *correct* if it corresponded to the reference diagnosis in every respect

(*b*) *doubtful* if it had been impossible to choose be tween several diagnoses provided that the various pos sibilities put forward including the true diagnosis

(*c*) *false positive* if a non-existent tumor was described on the echogram

(*d*) *false negative* if an existing tumor was not observed on the echogram and lastly

(*e*) *mistaken* if one tumor was mistaken for another (uterine leiomyoma instead of a solid tumor of the ovary for instance)

The same method was used to analyze the value of the clinical diagnosis (CD) It should be noted that the clinical diagnoses mentioned were generally made after the usual clinical examination and in most cases before any further exploration

RESULTS

The breakdown of the lesions defined according to the operative and microscopic descriptions such as leiomyoma cyst polyp is shown in detail in Table I together with the number of correct mistaken doubtful false positive and negative diagnoses from both clinical and ultrasonic examinations

In all the ultrasonic diagnosis (USD) is fully cor rect in 80% of the cases doubtful in 5% mistaken in 6% false positive in only 2% and false negative in 7%

Regarding the size of the tumors found during laparotomy (Table II) it will be remarked that only tumors of over 2 cm were successfully interpreted by ultrasound Apparently therefore masses of less than 3 cm cannot be distinguished by ultrasonic exploration in view of the high frequencies applied ($2 \cdot 10^6$ Hz) it is not a question of resolution power



Fig 1 Uterine leiomyoma (*F*) (12×11×11 cm) at least one subserous fibroid (*f*) is visualized to the right on transverse scan High signals amplification but weak echos from tumor distal boundary (arrow)



Fig 4 Polycystic ovary (9×7 5×6 cm)

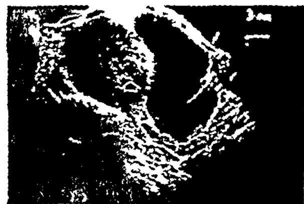


Fig 2 Uterine leiomyoma (12×6×9 cm) with edematous degeneration echos inside and cystic areas (arrow)

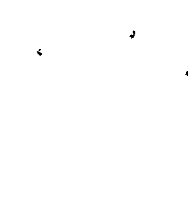


Fig 5 Dermoid cyst in the Douglas pouch (typical ... lar pattern left cystic pattern right)



Fig 3 Ovarian cyst (3×3×3 cm) (arrow)



Fig 6 Cyst adenocarcinoma (1?×9×7 cm) ... and polypoid patterns



[Fig] 7 Ovarian carcinoma (9×7×7 cm) ascites (*A*) and [perito]neal metastasis (*M*)



Fig 9 Bilateral pyosalpinx (3×2×2 cm) (arrows)



[Fig] 8 Uterine leiomyoma (*F*) and polycystic ovary (*O*) [Com]pare differences in sound attenuation by the amount [of ec]hos behind the two different kinds of tumors



Fig 10 Tubal pregnancy (arrow) and blood collection in Douglas pouch (*D*)

[O]n the other hand the tissues surrounding the [ova]ries and Fallopian tubes (parametrium in[testi]ne etc) are liable to disguise small swellings [whi]ch are sometimes visible on the echogram but [are] hard to interpret As regards the small [leio]myomata many of them were in intra[myo]metrial positions and others were subserous [Pos]sibly they escaped the examiner because the [scan]s were too far apart Thus if one disregarded [tum]ors measuring less than 3 cm the rate would [reac]h an excellent level of 98% correct ultrasound [diag]noses in the case of leiomyomata and ovarian [cys]ts These observations likewise relate to tubal [swe]llings It would be interesting to detail the clini[cal] circumstances for the 70% of mistaken doubt[ful] or false positive or negative diagnoses We shall [con]fine ourselves to a brief comment on Tables III IV and V which tabulates the clinical and ultrasonic diagnoses in a double entry form

(*a*) the two mistaken clinical diagnoses (CD) were pregnancy of about three months

(*b*) the 8 leiomyomata were clinically diagnosed five times as an ovarian cyst and three times as a pregnancy ultrasound read them eight times as a normal uterus

(*c*) in these two cases the leiomyomata measured less than 3 cm and the pelvic organs were judged to be normal by ultrasound

(*d*) the CD was leiomyoma

(*e*) the ultrasonic diagnosis (USD) was ectopic pregnancy six times and fluid filled tumor twice the CD was leiomyoma (7 cases) and ectopic pregnancy (1 case)

Table I *Ultrasonic and clinical versus pathology findings*

Organs	Pathology findings	No of cases	Ultrasonic findings: Correct	Mistaken	False +	False −	Doubtful	Clinical findings: Correct	Mistaken	False +	False −	Doubtful
Uterus	Leiomyoma	152	142	0	0	10	0	76	10	0	0	[illegible]
	Polyps	4	2	0	0	1	1	0	[illegible]	0	0	[illegible]
	Adenocarcinoma	6	0	2	0	0	4	0	5	0	0	[illegible]
	Pregnancy	1	1	0	0	0	0	0	1	0	0	[illegible]
	Total	163	145	2	0	11	5	76	8	0	10	[illegible]
	%	100	88 96	1 23	0	6 75	3 07	46 63	4 91	0	6 13	[illegible]
Ovaries	Cyst	114	96	12	0	5	1	35	[illegible]	0	0	[illegible]
	Solid tumor	22	14	3	0	3	2	0	6	0	3	[illegible]
	Cystoadenocarcinoma	12	12	0	0	0	0	0	0	0	0	[illegible]
	Total	148	122	15	0	8	3	35	18	0	3	[illegible]
	%	100	82 43	10 14	0	5 41	2 03	[illegible]	[illegible]	0	2 03	[illegible]
Tubes	Ectopic pregnancy	27	10	6	0	2	9	10	5	0	[illegible]	[illegible]
	Pyohydrosalpinx	11	7	0	0	3	1	3	7	0	0	[illegible]
	Total	38	17	6	0	5	10	13	[illegible]	0	2	[illegible]
	%	100	44 74	15 79	0	13 16	[illegible]	34 21	31 58	0	[illegible]	[illegible]
Miscellaneous	Ascites	6	5	0	0	1	0	1	[illegible]	0	1	[illegible]
	Intestinal obstruction	1	0	0	0	1	0	0	1	0	0	[illegible]
	Normal pelvis	14	7	0	7	0	0	0	0	14	0	[illegible]
	Total	21	12	0	7	2	0	1	3	14	1	[illegible]
	%	100	57 14	0	33 33	9 52	0	4 76	14 28	66 67	[illegible]	[illegible]
	Total	370	296	23	7	26	18	[illegible]	41	14	16	[illegible]
	%	100	80 0	6 2	1 9	7 0	4 9	33 8	11 1	3 8	43	[illegible]

(*f*) the USD was ectopic pregnancy (3) and hydrosalpinx (1) while the CD hesitated between tumor and ectopic pregnancy (3) and between leiomyoma and cyst (1)

(*g*) normal pelvis according to ultrasound

(*h*) in all three cases ultrasound interpreted the pelvis as normal while the clinical diagnosis was leiomyoma (2) and an ectopic pregnancy (1)

(*i*) the pelvis was normal on ultrasound whereas the clinical interpretation was cyst ectopic pre[illegible] nancy mass

(*j*) neither ultrasound nor the clinical diag[illegible] distinguished between a subserous leiomy[illegible] an ovarian cyst

(*k*) in every case there was excellent agree[illegible] between the CD and USD ectopic pregnancy [illegible] ascites (1) pyosalpinx (?)

(*l*) in all 9 cases including solid ovarian tu[illegible]

Table II *Tumor size*

Ultrasonic diagnosis	Less than 1 cm	1–2 cm	2–3 cm	3–4 cm	4–5 cm	More than 5 cm	Total
Ovarian cysts							
Correct	0	0	7	6	9	74	96
Error	8	9	1	0	0	0	18
Total	8	9	8	6	9	74	114
Uterine leiomyomata							
Correct	0	0	8	15	13	106	[illegible]
Error	4	4	2	0	0	0	10
Total	4	4	10	15	13	106	[illegible]

e III *Uterine leiomyomata*

	Clinical diagnosis					
...sonic ...osis	Correct	Mistaken	False +	False −	Doubtful	Total
...ct	76	[illegible]	–	–	64	14?
...aken	–	–	–	–	–	–
+	–	–	–	–	–	–
−	–	8	–	–	2	10
...tful	–	–	–	–	–	–
...l	6	10	0	0	66	15?

...ee text

e IV *Ovarian cysts*

	Clinical diagnosis					
...sonic ...osis	Correct	Mistaken	False +	False −	Doubtful	Total
...ct	34	1	0	0	61	96
...ken	0	8	0	0	4	12
...+	0	0	0	0	0	0
...−	1	3	0	0	1	5
...ful	0	0	0	0	1	1
...l	35	12	0	0	67	114

...e text

pyosalpinx (4) ascites (1) and pregnancy (1)
...l were correct and CD mistaken (2 ectopic ...nancies 3 ovarian cysts 4 uterine fibroids)
...l) CD was pelvic tumor in 7 cases whereas ...s was described as normal by ultrasound ... surgical procedures (laparotomy or laparos...y)

...) 1 case of *moderate* ascites was diagnosed by ...sound and *confirmed* by laparotomy whereas ...was only abnormal *pelvis*

...) *doubtful* CD in 28 cases in which USD was ...ect 12 ovarian cystoadenocarcinomas 11 ...rian solid tumors 2 endometrial polyps 2 cases ...ites and 1 pyosalpinx

...) these 11 cases were *mistaken* as well after ...asound as by clinical examinations respectively ...ollows 3 ovarian solid tumors 2 *cysts* and 1 ...oadenocarcinoma (USD) and 3 ovarian cysts ...) 4 ectopic *pregnancies* 3 ovarian cysts 1 ...rian solid mass (USD) and 3 leiomyomata 1 ...rian cyst (CD) 2 pyosalpinx and 2 endometrial ...cers mistaken and described after ultrasound ... clinical examinations such as 2 ectopic preg...cies and 2 uterine leiomyomata

(*r*) ectopic pregnancy (2 cases) considered as tubal masses (CD) and as hydro pyosalpinx (USD)

(*s*) 7 normal cases (laparoscopy) whereas USD was possibility of small cysts (3)—ectopic pregnancy (2) solid ovarian cyst (2) pelvic mass (7) for CD

(*t*) in 1 case of tubal abcess USD was normal pelvic status CD as correct

(*u*) USD was no pelvic tumor seen CD was ovarian cyst (1) leiomyoma (1) and pelvic mass (1) when laparotomy and microscopic findings were ascites (1) intestine obstruction (1) and uterine polyp (1)

(*v*) 2 cases of ectopic pregnancy and 3 cases of solid ovarian tumors were erroneously interpreted as normal pelvis after 1st clinical and ultrasonic examinations

(*w*) these 6 cases were mistaken (CD) and doubtful (USD) 1 uterine polyp polyp or very early pregnancy (USD) and uterine leiomyoma (CD) 1 ectopic pregnancy and 1 pyosalpinx 2 hydropyosalpinx or ectopic pregnancies (USD) and ovarian cysts (CD) 3 adenocarcinomas uterine leiomyomata or cancers (USD) and uterine leiomyomata (CD)

(*x*) neither USD and CD were able to state precisely the correct diagnosis in these 11 cases 8 ectopic pregnancies 2 solid ovarian tumors and 1 ovarian cancer

The *sensitivity* of ultrasonic diagnosis or the ability of the examination to produce a positive finding in a genuinely positive situation was calculated

It was also considered useful to test the *specificity* of ultrasonic diagnosis or its ability to produce a negative finding in a genuinely negative situation In view of the uncertainty caused by the fact that no

Table V *Miscellaneous*

	Clinical diagnosis					
Ultrasonic diagnosis	Correct	Mistaken	False +	False −	Doubtful	Total
Correct	13[k]	9[l]	7[m]	1	28	58
Mistaken	0	11	0	0	2	13
False +	0	0	7	0	0	7
False −	1[s]	3	0	5	0	9
Doubtful	0	6[w]	0	0	11[x]	17
Total	14	29	14	6	41	104

k–x see text

check could be made in 149 cases where surgery was not indicated it is impossible to state that in fact there was no lesion

COMMENTS

It can be seen from analysis of the cases dealt with that exploration by ultrasound is of great value in diagnosing the presence of a tumor in the pelvis particularly where the tumor diameter is greater than 2 cm In such cases the sensitivity of the echographic description is close to 0 98 It is also very accurate in cases of ascites The rate of correct ultrasonic diagnosis is lower for ovarian cysts than for uterine leiomyomata (84% against 93%) Furthermore it is also lower for all ovarian tumors than for tumors in uterine origin (82% against 89%) The difference in the results probably stems from the fact that where solid tissue is concerned only two out of three ovarian tumors are correctly diagnosed since this type of tumor is often described as a uterine leiomyoma on the echogram The high rate of correctly diagnosed cystadenocarcinomas is due to the fact that this type of tumor which usually contains several cystic loculi and numerous vegetations displays a highly characteristic pattern under ultrasound

As to ectopic pregnancies one can see how essential it is to know the patient s history since in another set of 87 patients (11) examined for specific reasons such as amenorrhea pain or haemorrhage the ultrasound sensitivity level is 0 82 against 0 37 in the present set

Thompson et al have published in 1967 a series of 100 patients with 63 good ultrasonic results (14) Hollander in 1968 has confirmed by ultrasound the presence as the absence of a tumor in 103 of the 114 studied cases (3)

In a very recent study Cochrane & Thomas (1) reported 82% correct diagnoses by ultrasound (80% in our series) but confined themselves to describing the size nature and uterine or extra uterine location of the lesions observed It appears however that these authors met with the same difficulties of interpretation more particularly in regard to solid tumors of the ovary Comparison with the initial conclusions of the clinician shows that ultrasonic examination comfortable and danger free for the patient is the ideal complementary exploration for refining a diagnosis

Ultrasonic exploration misses only 7% of the cases where a tumor is present (usually measuring less than 3 cm) and the echogram indicates a non existent tumor in less than 2% of the cases. Without resorting to other methods of gynecological diagnosis (i e X ray hysterosalpingography laparoscopy etc which still need to be used in all doubtful cases) simply by coupling ultrasonic exploration with the usual clinical diagnosis made in the consulting room the rate of false results can decrease considerably

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VIDEO DISPLAY SYSTEM FOR FETAL AND MATERNAL MONITORING

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...ct Signals from different fetal and maternal ...ring equipment were combined in a video system ...ve curves and digital figures were displayed on the ...creen and included warning signals Sweeps for ...nt curves are selected individually It is possible to ...ast and slow changing parameters on the same ... The system has great flexibility and signals from ...ment from different manufacturers may be added

...se of electronic equipment in monitoring the ...ion of the fetus has been established as an ...tant tool in the obstetrical clinic An ...tant advantage is the instant calculation of the ...eart rate (FHR) based on a single beat to beat ...al and the simultaneous recording of uterine ...y Our present clinical use of these recordings ...marily based on the relationship between ...es in FHR (decelerations and accelerations) ...hanges in the intrauterine pressure (IUP)

...tronic monitoring in obstetrics is still a ...ely young field and it is reasonable to expect ...much more information can be obtained by ...ning FHR and IUP with other parameters It ...en suggested that there may be an important ...n between maternal respiration and FHR or ...en IUP and fetal pH However with the ...t type of equipment it is difficult to obtain ... or other combinations of parameters in a ...ably simple way both from an economic and ...cal point of view

...ring the planning phase of the new University ...tment of Obstetrics and Gynecology at the ...v County Hospital a video display system has ... developed and clinically evaluated This system has great flexibility A combination of parameters from different types of equipment is easy and transmission of the information is performed by a simple coaxial cable

SYSTEM DESIGN

The video picture is composed in the *video mixer* which receives video signals from the five sources (Fig 1)

(1) *Patient data date and time* are supplied by the central hospital computer or by a TV camera watching a digital clock and a sheet with patient data and calibration lines

(2) *Dynamic signals* such as FHR IUP fetal and maternal ECG respiration frequency are supplied from bedside equipment and converted in an 8 channel analogue video converter (AVC 800)

(3) *Static signals* such as pulse rate temperature instantaneous FHR may be supplied from bedside equipment or from electronic equipment measuring pH pO_2 or pCO_2 Static signals are converted in a digital video converter (DVC 48) and displayed on the screen next to the corresponding text

(4) The primary parameters from the delivery room and the laboratory may pass through a *computer* such as a Corometrics minicomputer DPAC or the Hewlett Packard 5600 system and these results can then be shown on the video screen

(5) A camera placed in the delivery room makes it possible to show a *picture of the mother or new born* superimposed on the curves and figures or as alternatives to these

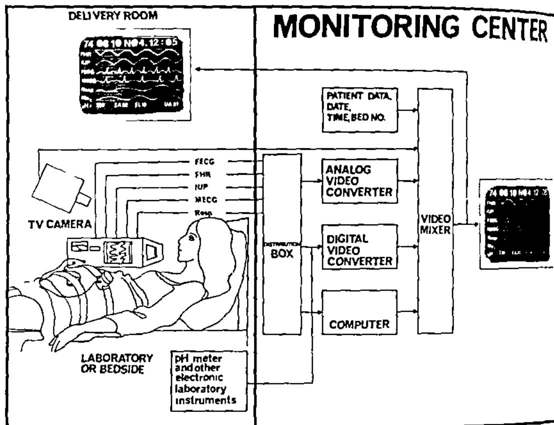


Fig 1 Block diagram of the system design The primary signals from the electronic equipment at bedside and from the laboratory are converted to video signals by the analogue video converter and the digital video converter These signals are mixed in the video mixer with patient data time indication and results from the computer A camera may add a picture of the mother or newborn The video picture contains in this case Date bed number time FHR and IUP as trend curves (previous 30 [illegible] EECG and MECG (previous 5 seconds) [illegible] showing maternal respiration and transcutaneous [illegible] tension (previous 30 minutes) previous fetal pH [illegible] computer data (early deceleration area late [illegible] area and uterine activity) The video picture is [illegible] monitor in the central monitoring centre as well as [illegible] bedside

MONITORS AND VIDEO PICTURE

The video picture is shown on a monitor in the central monitoring centre and is transmitted by a coaxial cable to a medium size (12") monitor at the bedside The video picture can also be transmitted to any place in the hospital by coaxial cables Monitors are placed in conference rooms lecture rooms and in the doctors offices (Fig 2)

Sweep speeds between 2 5 seconds and 8 hours may be selected individually for each of the 8 channels The immediate values are presented at the right edge of the monitor and shifted to the left at a rate determined by the sweep speed selected for the channel This storing capacity is due to the 8 memories in the AVC 800

It is possible to include alarm functions. If [illegible] FHR passes upper or lower limits the [illegible] indication of FHR will flash on the screen [illegible] warning systems may be designed for [illegible] uterine tonus excessive or strong [illegible] contractions or when the computer data [illegible] pathological conditions (e g decelerations [illegible] abnormalities)

RECORDING

Recording of data is valuable for routine [illegible] training and research The video picture can [illegible] recorded in four different ways (Fig 2)

(1) Polaroid photographs of the screen

(2) Paper copies produced in a Video Hard C[illegible] unit

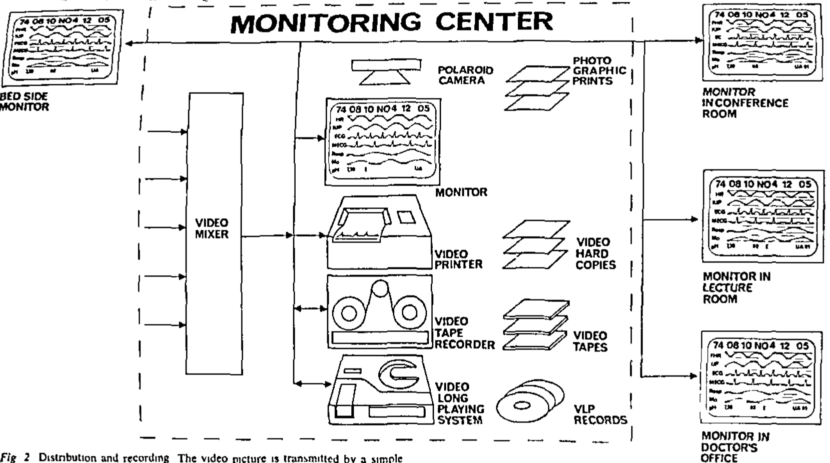


Fig 2 Distribution and recording The video picture is transmitted by a simple coaxial cable and may be shown at any place in the hospital for ex nuple in conference rooms lecture rooms and offices The signals are recorded on Polarcid photographs video hard copies video tapes or video long playing records When *using the last two methods the signals can be demonstrated on monitors on later* occasions for training or research

(3) Recording on Video Tape Casettes

(4) Recording of Video Discs on a Video Long Playing Recorder (not yet available)

The two last types of recording are preferable because they permit the data to be presented on monitors on later occasions as training or research material

COMMENT

The system has been evaluated clinically in the department during the past three months in daily routine use It is easy to use after a minimum of instruction The doctors mid wives and nurses have found the system valuable The patients have reacted very positively because they were able to follow the recordings on the bed side video screen This assured them that everything was under control

The video system has a number of advantages compared with conventional monitoring systems using trend scopes or paper recorders The primary parameters may come from equipment of different types In our preliminary system assembly the fetal monitoring equipment was a Hewlett Packard cardiotocograph type 8020 A and the maternal parameters (MECG pulse respiration etc) were measured at Philips Medical System modular units

Analogue curves and digital figures are displayed on the same screen and include warning [illegible] the form of flashing figures As sweep [illegible] different curves are selected individually [illegible] possible to show fast and slow changing [illegible] on the same screen (FECG and FHR) [illegible] features give a great flexibility and [illegible] equipment from different manufactors may [illegible] added easily

The recording methods are simple and [illegible] documentation training and research. The [illegible] data and time unit ensures the identification

The price of the system will not exceed [illegible] conventional monitoring system with a [illegible] number of read-out facilities The digital [illegible] may serve up to 8 beds with 6 sets of data for [illegible] patient The video converter may be shared by [illegible] delivery rooms with 4 channels each Further [illegible] expensive memory trend scopes of the [illegible] systems can be replaced by simple video [illegible] because of the memory capacity of the [illegible] video converter

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PREVENTION OF INTRAPERITONEAL ADHESIONS BY DEXTRAN HYDROCORTISONE AND CHYMOTRYPSIN[1]

An Experimental Study

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…act The purpose of an experimental study in guinea …was to prevent adhesion formation in the intra …neal space by simultaneous intraperitoneal infusion …drocortisone dextran and chymotrypsin An exami… made three weeks after the operation revealed a …y significant ($p<0.001$) difference in favour of the …an dextran-chymotrypsin and dextran chymo… …n hydrocortisone groups when compared with the …l and control groups

…occurrence of postoperative adhesions after …cal and gynaecological laparotomy varies …lly Often the adhesions lead to complications …secondary disease (18 19) Corticoids macro…cular dextrans hyaluronidase and fibrinolytic …tances are known to inhibit adhesion formation …ome ext nt (1 2 3 4 5 6 9 10 11 12 13 15 17)

…order to be able to minimize adhesion forma… following operations for sterility animal ex…ments were performed in an attempt to prevent …l abdominal adhesions

MATERIAL AND METHODS

Guinea pigs weighing 85–475 g were used 201 ani… were divided into experimental groups with 39–42 …ea-pigs in each group The following substances were …l for intraperitoneal injections Group 1 no injection …trol group) Group 2 Isotonic NaCl 10 ml Group 3 …tran 10 ml Group 4 Dextran 10 ml+Chymotrypsin …units Group 5 Dextran 10 ml+Chymotrypsin 25 …s+Hydrocortisone 10 mg

…extran=Rheomacrodex® Leiras Hydrocortisone= …dro-Adreson® Oy Organon Ab Chymotrypsin= …mar® Armour Pharmaceutical Company Ltd

62863

Operative technique

The animals were anesthetized with ether Their skin was shaved thoroughly cleaned sprayed with a plastic skin dressing (Nobecutan® AB Bofors) and covered with a split towel Sterile instruments were used but strict aseptic conditions could not be maintained The abdomen was opened with a short midline incision through which the caecum was pulled out Trauma likely to lead to adhesion formation was caused by exerting intensive pressure for 10 seconds with a Kelly s hemostat on the caecum at three sites about 5 mm apart The caecum was then replaced in the abdominal cavity and the peritoneum and the muscular layer were closed with a continuous 00 catgut suture through the fascia the outer muscle layer Immediately before the peritoneal suture was closed the test substance was injected intraperitoneally Care was taken to avoid spilling any liquid in the wound The skin was closed with interrupted silk sutures No antibiotics were administered post-operatively The experimental animals were killed three weeks after the operation their abdomens opened and the number and localization of adhesions recorded In order to exclude the possibility of bias the animals were examined without knowing the experimental group to which they belonged

Numerical values were given to the different grades of adhesions as follows no adhesions 0 1 very thin (hair line) adhesion=1 thicker distinct adhesion= two very thin adhesions=3 two thick or several adhesions=4

For statistical analysis Student s t test was used

RESULTS

The extent of adhesions in the 201 guinea pigs belonging to the five experimental groups is presented in Table I

The number of adhesions in the dextran groups was significantly smaller ($p<0.001$) than in the control group Even the difference between the NaCl and the control group was in favour of the NaCl group ($p<0.001$) The difference between the dex…

Table I. *Results of the degree of adhesions in the control and the experimental groups*

0 = no adhesions, 1 = very thin (hair line) adhesion, 2 = thicker, distinct adhesion, 3 = two very thin adhesions [illegible] thick or several adhesions

	No. of animals	Degree of adhesions					Mean value	Stand. deviat.
		4	3	2	1	0		
Control groups	39	19	10	10	–	–	3.23	0.84
Isotonic NaCl	42	16	6	12	8	–	2.71	1.17
Dextran	41	5	5	6	8	16	1.38	1.29
Dextran + chymotrypsin	39	6	–	12	8	13	1.47	1.34
Dextran + chymotrypsin + hydrocortisone	40	1	7	8	4	20	1.18	1.74

tran groups and the NaCl group was statistically highly significant in favour of the dextran groups ($p < 0.001$). No significant differences between the dextran groups could be demonstrated. Nevertheless, in Group 5, in which chymotrypsin and hydrocortisone were used in addition to dextran, numerous adhesions were found in only one case. More than half of the animals were free from adhesions.

DISCUSSION

Our study definitely indicates the superiority of dextran over isotonic NaCl and absence of treatment in the prevention of adhesions, even though Aszodi et al. (1) could not demonstrate in their cat experiments that dextran was better than NaCl. On the other hand, Kapur et al. (9) obtained better results in preventing adhesions with dextran than in their control groups. Several investigators have additionally demonstrated the definite adhesion preventing effect of cortisone and hydrocortisone (4, 5, 11).

Swolin's studies (16) demonstrate conclusively that hydrocortisone administered in relatively massive doses, in the investigations performed so far, is effective in the prevention of intraperitoneal adhesions. Totterman & Arstila (20) have demonstrated that dextran definitely remains in the abdominal cavity for a longer period than physiologic saline and proposed that other substances infused into the abdominal cavity together with dextran would also remain there for a period longer than normal. Knightly et al. (12) used fibrinolysin and heparin to prevent adhesions and found that the best results were obtained by using the two substances simultaneously. In the hydrotubation of sterility patients, Grant & Robertson (7) used [illegible] amounts of hydrocortisone and chymotryps[illegible] obtained relatively good results in comparison [illegible] the control series. The simultaneous admi[illegible] of three adhesion preventing substances is [illegible] ently exceptional, but as our primary res[illegible] guinea pigs have been promising, they [illegible] us to continue our studies in clinical work [illegible] in the operative and postoperative thera[illegible] sterility patients and in cases of ectopic pregn[illegible] by infusing them intraperitoneally with [illegible] combination before the final peritoneal closure [illegible] later by daily hydrotubations.

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An International Symposion on Hypertensive Disorders in Pregnancy will take place in Muenster Westf Federal Republic of Germany August 24–26 1976

The following topics will be discussed Morphology of the Kidney Pathophysiology Endocrine aspects Placenta and uterine blood flow Treatment aspects and nomenclature Free communications will be presented only in a limited number Languages English and German

For information write to the Congress Secretary Heinz D Böttcher M D Universitats Frauenklinik Westring 11 4400 Munster/Westf Federal Republic of Germany

The 5th International Conference on Birth Defects will take place in Montreal on 21–27 August 1977 Organizing body National Foundation—March of Dimes

Further information can be had from the Secretariat c/o Holland Organizing Centre 16 Lange Voorhout The Hague the Netherlands

The International Society for Twin Studies announces the *Second International Congress on Twin Studies* to be held in Washington D C USA 29 August–1 September 1977

Further information can be obtained from Dr Gordon Allen Second International Congress on Twin Studies Clinical Center 2N252 National Institutes of Health Bethesda Maryland 20014 USA

German society for endocrinology
Competitions for 1977

Award Schoeller Junkmann Award
Amount DM 15000 –
Donor Schering AG Berlin
Applicants must reside in Europe and not be older than 40 years
Subjects all fields of endocrinology (except diabetes mellitus)
Award Marius Tausk *Career Development Award*
Amount DM 15000 –
Donor Organon G m b H Munich
Applicants must reside in Europe and not be older [illegible] 33 years
Subjects clinical and clinical-experimental endocri[illegible] logy (except diabetes mellitus)

Applicants are invited to submit two copies of [illegible] viously unpublished papers in either German or Eng[illegible] together with a short curriculum vitae and a descrip[illegible] of the development of their scientific career [illegible] President of the German Society for Endocrinology [illegible] 1976/77 Prof Dr med Gerhard Bettendorf [illegible] täts Frauenklinik Martinistraße 52 2000 Hamburg [illegible] later than October 15 1976

After receipt of the manuscript has been [illegible] edged by the German Society for Endocrinology [illegible] author is at liberty to have his paper published [illegible] periodical

Detailed information concerning the awards [illegible] obtained from the President of the Society The [illegible] will be presented at the 22nd Symposium of the Ger[illegible] Society of Endocrinology 1977

As a tribute to Rene Moricard

Associate Professor in Hormonology at the Facu[illegible] Médecine de Paris his friends have decided to [illegible] a prize of 125000 B F The best experimental work [illegible] ing to the Initial Stages of the Cancer of the Ut[illegible] Cervix will be awarded with this prize Only [illegible] research on this topic will be considered. An [illegible] having already been awarded a prize will not [illegible] contemplated

At the latest on December 1 1976 manuscripts [illegible] be in the hands of Doctor R Vokaer [illegible] Obstétricale et Gynécologique Hôpital Unive[illegible] Brugmann Place Van Gehuchten 4 1020 Br[illegible] *Belgium*

Acta Obstet Gynecol Scand 55 275–278 1976

THE EFFICACY OF MELPHALAN IN THE COMBINED CHEMO THERAPY OF MALIGNANT TROPHOBLASTIC DISEASE

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i Steadily progressive improvement in the stic and therapeutic management of malignant lastic disease has occurred over the last few de The most important diagnostic aid is the determina serum HCG by sensitive radioimmunoassay which the detection of minute amounts of the hormone mits discrimination between LH and HCG Thera advances include the use of combinations of differ ostatic drugs which have increased the cure rate proximately 50% to a range of 80–95% (1 2 3 4) Malignant trophoblastic disease is rare in the navian countries which effectively limits oppor to acquire experience within individual centers ter a series of 3 cases has been collected at the ska Hospital during the last 10 years Patients who ped resistance against methotrexate were success eated by a combination of an alkylating agent mel (Alkeran) actinomycin D and methotrexate In ses this modification of a triple therapy regimen ned out to be life saving

MATERIAL AND METHODS

ines consisted of 23 women 11 of whom displayed of metastasis at the time of initial discovery Suspi f molar disease was noted in 15 patients after in ental evacuation spontaneous abortion in three and regnancy in another three

l diagno s of malignant trophoblastic disease was on a generally accepted parameter i e serum HCG persisting without definite decline of the titer or sing bey nd an observation period of 2 months fol instrumental evacuation of a molar pregnancy or ing secondary to spontaneous abortion or term de Pers tent uterine hemorrhage sub-involution of rus pathologic findings in uterine curettings indi (malignancy pelvic arteriography radiograph of the and scintogram of the liver and the brain were used ditional diagnostic criteria although the presence of in serum always was required as proof of malig

e regimen of the triple therapy course consisted of sually prescribed doses of methotrexate and actino D given over a 5-day period In addition melphalan was administered by intravenous infusion for 6 hours on the first treatment day Modification of th indi idu l doses for subsequent courses was m de after a ssing any toxic symptoms or signs generall by a lower g f the melphalan dose Details of th triple therapy regim n are shown in Table I

RESULTS

The distribution of the case material betw e metastatic and non metastatic conditio as v el the overall therapeutic results appe r ir Tabl

One patient 44 years of age develop metastases following a molar pregnanc ceived various combinations of chemo agents including methotrexate actinom D and chlorambucil Methotrexate was also adr inistered as a regional infusion and hysterectomy and ne phrectomy were performed as part of the tre t ment In spite of intense therapy the patient did not survive Autopsy showed multiple metastases of choriocarcinoma in the lungs brain liver kidney and vagina A subsequent patient who developed resistance to methotrexate and actinomycin D and in whom appared signs of increasing pulmonary metastases served as the first candidate to be given the new combination of chemotherapy which proved to be very effective

Table I *Triple therapy regimen applied in cases resistant against conventional methotrexate therapy*

Methotrexate	12 5 mg×2 i m /day over 5 days
Actinomycin D	0 5 mg i v /day over 5 days
Melphalan	1 0 mg/kg in 500 ml glucose solution I v infusion during 6 hours on the first treatment day

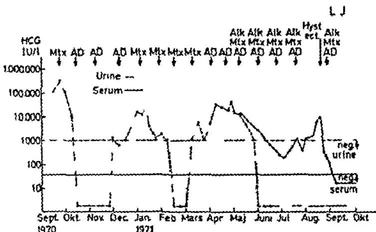


Fig 1 (Case 1) HCG levels and [illegible] treatment Mtx = methotrexate [illegible] tinomycin D Alk = melphalan [illegible] Hyst ect = hysterectomy Note that [illegible] ple therapy courses before hys[illegible] resulted in disappearance of the p[illegible] metastases

Case 1 (L J)

30 year old nullipara with three first trimester spontaneous abortions After the last miscarriage vaginal bleeding continued which required repeat curettage 2 weeks later *Pathologic examination of the specimen revealed signs of* malignancy and an X ray suggested pulmonary metastases Subsequent developments are illustrated in detail in Fig 1 The initial methotrexate and actinomycin D courses resulted in HCG negative urine Routine urine tests remained negative for a period of one month after which HCG reappeared Actinomycin D alone had no effect and repeated methotrexate courses resulted only in brief periods of HCG negative urine Ultimately complete drug resistance developed

Triple therapy using an intravenous *melphalan infusion* over a 6-hour period on the first day of a 5-day course with methotrexate and actinomycin D resulted in a rapid response such that urinary HCG became negative and remained so for several months It was noted also that the pulmonary metastases disappeared However the serum HCG assay which had not been available earlier showed that there was still *an active secretion of HCG in* spite of four additional triple courses and pelvic examina[illegible] revealed a persistently enlarged uterus These find[illegible] in addition to a steadily increasing serum HCG level [illegible]icated the necessity of a hysterectomy Surgery was performed 11 months after beginning methotrexate or three months following the first triple therapy course and resulted in a rapid decrease *and disappearance of HCG* The pathology specimen demonstrated the presence of a viable choriocarcinoma within the uterine wall Therapy was completed with a final triple therapy course and the patient has remained HCG negative for a 4 year period

Case 2 (E L 25 years)

A positive pregnancy test was present 10 weeks following instrumental evacuation of hydatidiform mole showing signs of moderate trophoblastic proliferation At pelvic examination there was a mass the size of a hen s-egg to the left of the uterus and pelvic arteriography revealed a vascular tumor in the same area Methotrexate 25 mg per day over 5 days and repeated one month later resulted in a rapid disappearance *of urinary HCG* but serum HCG remained at a level of 500–1 000 IU/l and tended to increase (Fig 2) Triple therapy with melphalan induced a[illegible] ous regression and serum became negative [illegible] one month following initiation of the course A [illegible] treatment course was given after which serum [illegible] *tions remained negative Four* months later the pa[illegible] became pregnant in spite of careful contraceptive [illegible] Legal abortion by vacuum aspiration showed a [illegible] conceptus and the patient has been healthy [illegible] over an observation period of 3 years

Case 3 (A L 29 years)

Four pregnancies of which two were benign hydatid[illegible] moles and one was a spontaneous abortion The la[illegible] pregnancy went to term and the patient was delivered [illegible] healthy boy (1971) In the spring of 1973 irregular [illegible] bleeding began and diagnostic curettage was perform[illegible] No signs of pregnancy were noted in the specimen [illegible] autumn of the same year vaginal bleeding recurred [illegible] another curettage was *performed* Microscopic exam[illegible] tion of the material showed chorionic tissue [illegible] tendency towards proliferation The urinary HCG [illegible] was 400 IU/l and an X ray film of the lungs show[illegible] presence of a small suspicious density The patient [illegible] referred from a community hospital to this de[illegible] On pelvic examination a marked enlargement of the [illegible] with only a slight *enlargement of the* uterine corpus [illegible] noted The cervical canal was open for more than [illegible] and the internal surface of the uterus was covered [illegible]

Table II *Malignant trophoblastic disease (Karolinska Hospital Stockholm 1966–1974)*

No of patients	23
Non metastatic	11
Metastatic	12
Etiology	
Mole	16
Abortion	3
Term delivery	4
Result	
Alive	22
Dead	1

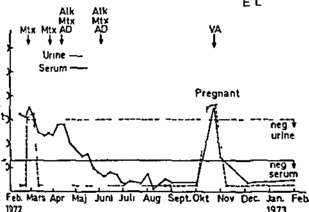


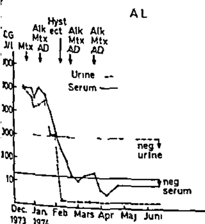
Fig 2 (Case 2) VA=vacum aspiration Note the tendency towards increasing serum HCG levels prior to the first triple course

ayer of tumor Serum HCG was high namely ≡IU/l The initial methotrexate course did not influ e serum HCG level and triple therapy was started eeks later (Fig 3) Serum HCG decreased marked intra uterine tumor became soft and diminished in Hysterectomy was performed as a safety measure o because of the patients previous two molar preg Microscopic examination of the uterus showed re non viable choriocarcinoma like tissue X ray ation of the lungs was negative ultimately and the has been healthy with HCG negative serum over ervation period of almost one year

(M B 21 years)

atient had a legal abortion in 1972 and was delivered ing a normal pregnancy in March 1974 She was ed 10 weeks postpartum due to profuse vaginal ng which required instrumental evacuation (June 4) The specimen revealed decidua and tropho- with atypical proliferation The serum HCG was not red unfortunately and three weeks later the patient developed acute lower abdominal pain Upon admission she presented with signs of a massive intra abdominal hemorrhage A decision to perform a laparotomy was made but an X ray film of the lungs taken immediately prior to surgery showed widespread pulmonary opacities strengthening the suspicion of metastatic trophoblastic disease and secondary perforation of the uterus The abdomen contained at least 1000 ml of blood and there was a small area of perforation on a walnut sized soft tumor in the fundus of the uterus In consideration of the patients age the tumor area was excised and the uterine wall sutured together in two layers The pathology showed a choriocarcinoma Serum HCG was 72000 IU/l on this occasion

Two courses of methotrexate later resulted in a signifi cant decrease of the serum HCG levels followed by a rise again (Fig 4) A triple therapy course induced a rapid fall in the titers and the HCG test became negative three weeks later A further triple therapy course was given one



3 (Case 3) The high initial HCG levels did not re d to methotrexate alone Note the rapid decrease in following the first triple course

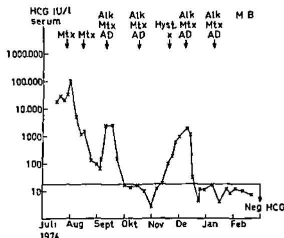


Fig 4 (Case 4) The patient developed resistance against methotrexate but responded favourably to repeated triple courses The pathology specimen did not show any rem nants of chroionic tissue

month later but following a period of three weeks HCG reappeared in serum and hysterectomy was performed (November 25 1974) since the uterus was slightly enlarged However microscopic examination showed no remnants of the tumor in the myometrium During the subsequent 14 days there was a further rise in the serum HCG levels and triple therapy was given again This time there was a rapid fall in HCG and the test became negative A fourth course was begun on January 7th 1975

The widespread pulmonary metastases decreased rapidly following the first triple course Doubtful pulmonary densities existed at the time of hysterectomy but the X ray films are perfectly normal at present The patient has been HCG negative for 6 months

The white cell and the platelet counts decreased in all patients following the triple courses and reached minimum levels at approximately 7–10 days following termination of the treatment cycle The decline of the values did not reach alarming levels in any instance and there were no signs of persistent damage to the hematopoetic system

DISCUSSION

Melphalan an alkylating agent has not been used to any extent previously in the treatment of malignant trophoblastic disease The only report that we have found described the successful use of this compound in two cases of choriocarcinoma like tumor of the testis (8) Chlorambucil and cyclophosphamide represent the common alkylating agents which have been utilized in combined therapy regimens of this disease The tumor suppressive effect of alkylating agents is rather similar for all the different compounds However minor differences with regard to half life time solubility and effects on the hematopoetic system do exist It can not be claimed that melphalan has advantages over lorambucil and cyclophasphamid either on the of theoretical considerations or clinical ex ience In spite of this it seems obvious that melphalan has a marked tumor suppressive effect in patients resistant to methotrexate The dose utilized certainly was well tolerated

In accordance with earlier experience the present series illustrates that hysterectomy need not be a primary step in the treatment of malignant – blastic disease Among our ?? patients fe could be maintained in 19 and on the ba s of pathology reports it seems that hysterec– unnecessary in two of the three patients T– sults also illustrate that surgery in spite of th cacy of modern chemotherapy may sti– important role in the management of – trophoblastic neoplasms

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CASF REPORTS

CHORIOANGIOMA WITH HYDRAMNIOS AND INTRA UTERINE FETAL DEATH

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Chorioangiomas are benign placental tumours from fetal vessels that occur with a frequency of nately 1% Often they are associated with nios and intra-uterine fetal death Based on a case ple chorioangiomas with a fatal course for the pects of the pathogenesis of hydramnios are dis Future development in ultrasound technology litate antenatal diagnosis

angiomas are benign placental tumours de rom the fetal vessels They are considered amartomas (3 8) In larger series they occur approximate frequency of 1% (10 13) The y measure a few centimetres across and are within the placental substance Large ngiomas (1 4 8) are rare whereas the relatively often is multiple (2)

noangiomas are frequently associated with nnios (33% of Sidall s (20) 110 cases 25% hnel s (7) 163 cases) Intra uterine fetal ratio is very high (35% of Strakosch s (11) ses)

paper illustrates a case of multiple chorioan s associated with fast developing hydramnios tra uterine fetal death Based on an analysis topography of the tumour certain aspects of thogenesis of hydramnios and the possibility natal diagnosis are discussed

CASE HISTORY

ear-old primigravida was admitted to the Depart of Obstetrics and Gynecology on December 23 hree weeks prior to the estimated date of delivery e of rapidly increasing hydramnios Her weight was (normal weight 50 kg) and the abdominal girth was m The single fetus (X rays) was in a cephalic position with a normal fetal heart rate The patient who showed no signs of preeclampsia or diabetes mellitus was not in labour

As the hormone analysis on a 24 hr urine sample would be delayed due to the Christmas holidays the patient was controlled daily with the cardiotocograph No signs of fetal distress were observed during the first 3 days On December 27 no fetal heart beats could be observed and amnioscopy showed meconium stained liquor amnii Emergency ultrasound scanning showed no fetal heart action polyhydramnios and a large placenta reaching from 10 cm above the symphysis to the uterine fundus (Fig 1) The delayed urine analysis showed oestriol 4 mg/24 hr Plasma chorionsomatomammotropin (HPL) was 16 4 μg/ml Labour was induced and the patient delivered a dead girl (3250 g 50 cm) At autopsy no abnormalities were found The heart weight was normal (16 g)

The placenta was large and oedematous measuring 21×20×4 cm weighing 1150 g The abundant membranes were discolored by meconium The cord which entered 4 cm from the margin measured 32 cm and contained three vessels Numerous parallel sections through the placenta revealed multiple typical chorioangiomas measuring from ½×½×½ cm to 3×4×4 cm The tumours were not spe

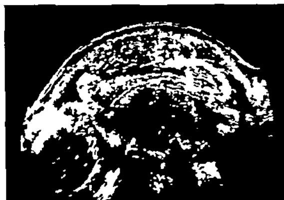


Fig 1

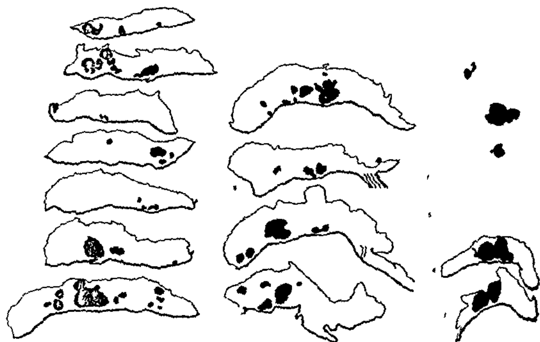


Fig 2

cifically concentrated around the entry of the cord (Fig 2) Microscopy (Fig 3) confirmed the diagnosis showing large trophoblast lined nodules packed with thin walled often dilated capillaries Many single terminal villi with numerous vessels were interspersed among normal villi Minor parts of the nodules showed hemorrhagic infarction

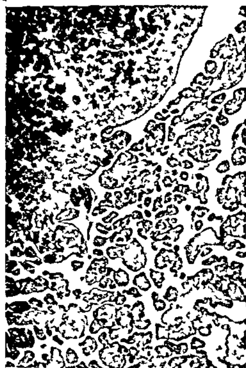
DISCUSSION

Studies on the mechanism of amniotic fluid formation (5) have shown that the exchange of liquor amnii in the so called three-compartment system (mother–fetus–liquor amnii) under normal conditions is by far largest between mother and fetus i e through the placenta With the rapid exhange rate of amniotic fluid (approximately one third of the total volume per hour (12)) even the slightest imbalance (few ml) in the normal exchange could result in accumulation of liquor due to a decrease in removal of or an increase in production of amniotic fluid

It must be stated however that the mechanism of the development of hydramnios is not settled even though it is clearly related to the chorioangiomas Kühnel (7) thought it to be due to venous obstruction within the placenta whereas Benson & Joseph (1) argued that the tumour growth increased the fetal surface of the amnion thereby increasing the production of liquor amnii Klaften (6) mentioned that hydramnios was more frequent the closer the tumour was situated to the entry of the umbilical cord thus causing strangulation of the large umbilical vessels Several authors [illegible] consider the chorioangioma a "dead space" which causes recirculation to the fetus of blood with low content of oxygen and other essential metabolites and still containing waste products

In the present case there was no close relationship to the entry of the umbilical cord (Fig [illegible] Based on a topographic examination the total amount of solid well defined nodules was [illegible] of the placental volume Microscopy however re-vealed that larger parts of the placenta between the tumours consisted of a mixture of normal villi and small chorioangiomas which often had partly preserved villous configuration If the microscopic findings are true for the placenta as a whole then the total mass of tumours must be close to half the placental volume thereby explaining its large size There was no general decrease in placental function since the HPL was relatively increased

The dead space theory seems to be a logical explanation for fetal distress where no strangulation of the large umbilical vessels could be demonstrated A change in normal circulatory conditions leading to excess strain on the fetal heart [illegible]



I

...t in intra uterine fetal death The heart will ...o maintain the normal blood volume of 400–500 ...inute by increasing its capacity The relative ...ia will further promote cardiac strain The ...al size of the infant heart could be explained ...e rapidly developing hydramnios

...hydramnios is not caused by anencephaly ...us immunisation twin pregnancy or diabetes ...itus then multiple or large solitary chorioan...as should be suspected At the present time ...sound scanning of the placenta will not reveal ...h but the placental size and position However ...en (1975) (personal communication) claims that ...tone scanning may in the future present a bet...icture of the placental interior thus making an ...natal diagnosis of chorioangioma possible

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BOOKS RECEIVED

Psychological Aspects of a First Pregnancy and Early Postnatal Adaption by P M Shereshefsky and L J Yarrow North Holland Publishing Company Amsterdam 1973 373 pp Price Dfl 38 00 US$ 14 60

This highly valuable book is unique in its disposition being intended for gynecologists general practitioners midwives psychologists but also for a more heterogenous public The book gives a profound analysis on various psychological factors having influence on the experience of pregnancy on delivery and on the postnatal period as well Furthermore the book evaluates not only the role of the mother in all these events but also the father s Considering the fact that the methodological part of the work is also of excellent quality this book constitutes an important achievement in the [illegible] preventive obstetrics

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45 XO TURNER s SYNDROME WITHOUT EVIDENCE OF MOSAICISM IN A PATIENT WITH TWO PREGNANCIES

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act A case of Turner s syndrome (45,XO) with two iancies is reported There was no evidence of mosai after chromosomal investigation of 5 different tissues aries blood skin uterus) Pregnancy occurred in cases after withdrawal of substitutional hormone py The first pregnancy ended with abortion of a rated hydrocephalic female fetus Chromosome es could not be carried out The second pregnancy d with delivery by caesarian section of a normal boy Y) Prenatal chromosome analysis was not carried or ethical reasons

itisfactory definition of Turner s syndrome is yet available The definition should include an ological explanation Ferguson Smith (3) has put ard the hypothesis that monosomy of the t arm of the X chromosome is the decisive or in the origin of the syndrome of short stature congenital malformations There is no agree t however on the number and character of ormations or the state of the gonads that is to ound

or these reasons and also because of its rarity it found of interest to publish a third case of so ed Turner s syndrome in which pregnancy oc ed Furthermore the case is of interest because chromosome complement of several tissues in ding both ovaries could be investigated and be se the patient got pregnant twice A more de d report of the hormonal investigation will be lished later

CASE HISTORY

patient is 14? cm high She has slight cubitus valgus no pterygium colli or other malformations have been d She is married

She was infantile without secondary sex characteristics when first seen 19 years ago but after being treated from her 15th year with synthetic oestrogens (and later genuine oestrogens) she developed sex characteristics and has had regular vaginal bleeding When 30 years old she suddenly stopped her hormone intake 3 months later she was found to be pregnant The diagnosis was established by means of ultrasound scanning (Fig 1) and elevated excre tion of oestriol (maximum 2 5 mg/?4 hrs)

A spontaneous abortion occurred in a hospital in an other part of the country at about 26 weeks of gestation The fetus was of female sex stillborn macerated and hydrocephalic It weighed 600 g and measured 34 cm No tissue was obtained for chromosome analysis

An exploratory laparotomy was carried out about a year later The uterus was found to be normal On the right side the gonad was represented by a streak 2 5× 0 5×0 5 cm In direct connection with this streak a cyst like structure 1 5 cm in diameter was found On the left side a very small but normal looking ovary was present though without visible follicles or corpora lutea (Fig 2)

Biopsies from the ovaries showed normal ovarian stroma with very few follicles on both sides Two pri mary follicles but no antral and Graafian follicles or cor pora lutea were found on step sections An atretic fol licle was seen in the biopsy from the left ovary (Fig 3)



Fig 1 Ultrasonography of uterus in about 20th week of the patient s 1st pregnancy showing the fetal head



Fig 2 Photograph of the uterus and ovaries during operation *Left* the small but otherwise almost normal ovary is seen *Right* the cyst is shown in close connection with the streak

As the patient hoped for another pregnancy stimulation therapy was carried out with large doses of gonadotrophic hormones stimulation had no effect and no elevation of oestrogens in the urine was found Vaginal bleeding recommenced following the stimulation however She started again on oestrogen therapy but stopped in December 1973 In February she took a few tablets but stopped again and had a vaginal bleeding In April 1974 she was again pregnant The uterus was enlarged quantitative

Table I *Results of chromosome analysis*

Tissue	<43	43	44	45	[illegible]	[illegible]
Patient 45 XO						
Peripheral blood (two cultures)		1	1	4[illegible]	[illegible]	[illegible]
Skin	1		3	36		[illegible]
Uterus			1	34		[illegible]
Right ovary		1	1	48		[illegible]
Left ovary				49	1	[illegible]
Total	1	2	6	201	1	[illegible]
Child (46 XY)						
Amniotic cells (7th month)					15	[illegible]
Blood (after delivery)					15	[illegible]

HCG showed 3700 IU/l Ultrasound scanning [illegible] established the diagnosis by showing a normal [illegible] configuration She was delivered by caesarean [illegible] a normal boy weighing 2900 g after about 9 [illegible] pregnancy during which she was admitted to the [illegible] and closely monitored by ultrasound urinary [illegible] cretion and serum HPL levels Apart from [illegible] complications occurred Alphafetoprotein in the [illegible] fluid was normal

Chromosome studies

The results of the chromosome studies are seen in [illegible] I Cells from the patient s peripheral blood skin [illegible] and both ovaries were investigated Blood was [illegible] twice A total of 215 mitoses were counted [illegible] 45 XO complement Only three of the non modal [illegible] 46 chromosomes One of these was from the [illegible] and had a 45 XO +E complement The other [illegible]

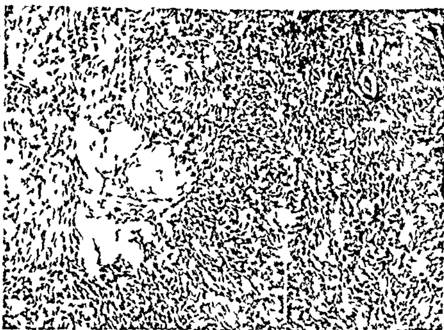


Fig 3 Biopsy from [illegible] showing two small [illegible] and an atr[illegible] [illegible] ows) H E x[illegible]

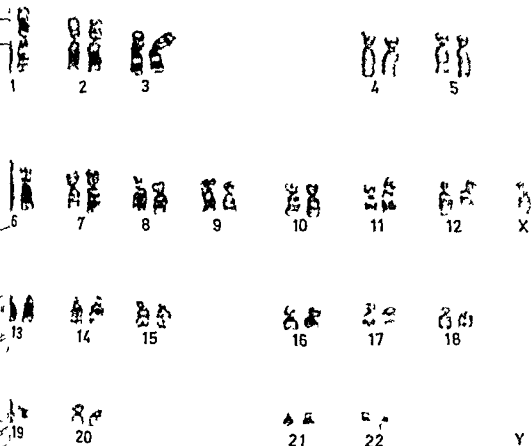


Fig 4 Karyotype from right ovary Trypsin–Giemsa showing 45 chromo omes One sex chromosome ...ing

blood and could not be analysed in detail (very old ...ration) The nine others had hypomodal numbers ...al smear showed no X or Y *chromatin*

...study of the karyotype of the patient did not reveal ...evidence of the presence of translocations including ...of th *missing* X chromosome (Fig 4)

...e chromosome *complement* of the fetus was studied ...mniotic cells in the 7th month of the pregnancy be...e of hydramnios *and too late* for interference (abor... and on blood after delivery *and* a *normal 46 XY* ...mosome constitution was found in both tissues

DISCUSSION

...as decided *not to* offer the patient an amnio...tesis in the second pregnancy because of the ...ous ethical problems involved in case of finding ...5 XO chromosome complement in the fetus ...en she developed hydramnios after 7 months ...asound scanning and amniocentesis was carried out with a view to examining alphafetoprotein con centrations in amniotic fluid At the same time a chromosome analysis was carried out because it was considered that a diagnosis of 45 XO in the fetus at that stage of pregnancy would not by itself indicate termination of the pregnancy She was de livered by caesarian section of a normal boy (46 XY) without congenital malformations

Since the end of the pregnancy the oestrogen ex cretion has been very low More than 7 months after delivery oestrogens in urine are at 4–6 μg/l A more detailed report of the hormonal status will be published elsewhere

It is well known that a missing X chromosome does not interfere with the presence of oocytes in the ovary as it has been shown that fetuses with 45 XO complement do have normal ovaries con taining germ cells in early fetal life (2) The disap pearance rate for germ cells must therefore be af

fected by the missing X or missing part of the short arm of the X chromosome The reason for this is unknown It is possible that some quantitative effect is acting and therefore rare cases such as the one published here are only representing an extreme variation of the normal picture of Turner s syndrome Mosaicism is another possible explanation Although this possibility is always present no evidence of mosaicism was detected by a study of five different tissues

Two other cases of Turner s syndrome in which pregnancies proceeded to term are reported in the literature (1 4) The present case is the only one where two pregnancies have occurred and where mosaicism is deemed highly improbable Several reports may be found in the literature of Turner patients having shown signs of some ovarian function (5) and therefore it does not seem reasonable to include streak ovaries in the definition of Turner s syndrome

ACKNOWLEDGEMENT

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A PROSPECTIVE STUDY OF DRUGS AND PREGNANCY

4 Miscellaneous drugs

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stract The results are presented of a prospective study drug use during pregnancy involving antibiotics anal ic drugs and iron and vitamin preparations The study s conducted in Malmo between 1963 and 1965 No favourable effect of the use of antibiotics mainly icillin and sulphonamides could be demonstrated iong 15 women who had an infant with hypospadias ee had used penicillin during the first trimester but this y well be coincidental Analgesic drug use shows a ability which resembles that previously described for chopharmaca *No effect on the malformation rate or* nt survival could be found A possible lengthening of mean duration of pregnancy occurred after the use of lgesic drugs during the 2nd or 3rd trimesters Women o are going to have a dead or malformed infant use iron l/or vitamin preparations less often during late preg y than women who prove to have a normal infant ien such drugs were used the percentage of preg cies ending in birth before the 38th week is reduced l the birth weight among term babies is higher The ociations between pregnancy outcome and the use of n and vitamin preparations is *probably indirect due to* ial factors associated with drug use

is paper reports data from a prospective study of ig use during pregnancy carried out in Malmo ring 1963–1965 In three earlier reports the use of ychopharmaca antiemetics and endocrine prep tions were described The present paper sum riz s data on miscellaneous drugs antibiotics algesics and *iron* or vitamin preparations i biotics have been studied for a teratogenic ef t (cf 5) and early claims exist *for such an effect* ! The harmful effect of tetracyclines on dental velopment has been demonstrated (15) and the ssibility that they can cause true malformations is ll open to debate (14) Some studies (e g 13) ggested that the use of analgesic drugs during early pregnancy may harm the embryo but others (4) could not verify this

MATERIAL AND METHODS

The study is based on information collected prospectively *from 6376 women The first paper of this series (8) de* scribes the details of the study

RESULTS

1 Antibiotics

Fig 1 shows the overall use of antibiotics during the *different months of pregnancy and according to* pregnancy outcome miscarriage or birth of a living infant Among a further 123 pregnancies ending in

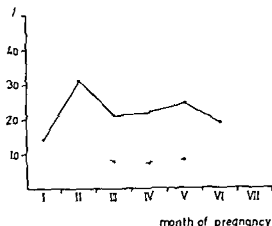


Fig 1 Percentage of women using antibiotics during dif ferent months of gestation —=miscarriage •=living infant

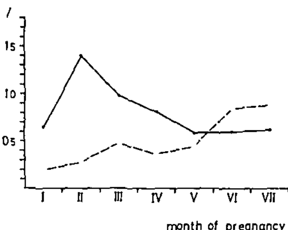


Fig 2 Incidence of recorded infectious diseases with fever (—) and of urinary tract infections ( ) during different months

an induced abortion antibiotics were used by a maximum of five women each month of pregnancy—a number too small to make comparisons meaningful Among 68 pregnancies ending with a stillbirth only two women used antibiotics

Fig 1 shows that women who will later miscarry show a markedly higher drug use than women who will later have a living infant For both categories maximum antibiotic use occurred during the second month of pregnancy Then 72 women who later had a living infant used antibiotics out of a total of 5684—among 417 women who later had a mis[illegible]riage 13 used antibiotics ($\chi^2=9\ 69$ at 1 [illegible] $0\ 01>P>0\ 001$) During the first month of preg[illegible]cy—i e before the first missed period—the [illegible]carriage group also shows more than double th[illegible]cidence of antibiotic use compared with the gro[illegible] live births but statistical significance is not reache[illegible] ($\chi=3\ 5$ after normal transformation at 1 [illegible] $0\ 1>P>0\ 05$) The reason for the peak inciden[illegible] antibiotic use during the second month is explained from Fig 2 showing the incidence of infection with fever—mainly upper respiratory tract infe[illegible]tions—and of urinary tract infections in the [illegible] series The former graph has a definite peak during the second month and then tapers off to a stead[illegible] state after the fourth month level with that of the first month Urinary tract infections increase in [illegible]cidence—or detection—during the whole of pre[illegible]nancy The main drugs used for these diseases are penicillin and sulphonamides Table I shows th[illegible] of these two drugs during the first trimester [illegible] the outcome of the pregnancy There are no [illegible]tions that either of the drugs is harmful for the embryo but so few cases are included that [illegible] marked teratogenic effect cannot be excluded from these data One interesting point is that among [illegible] pregnancies ending with the birth of an infant [illegible] hypospadias three had used penicillin during the first trimester

Table I *Number of women using penicillin or sulphonamides during the first trimester*

Infants with major malformations and matched controls infants without malformations but dead within one year [illegible] matched controls Expected numbers calculated from the incidence of antibiotic users in the total group of women [illegible] birth to non malformed infants (128/5 00?) or from all controls

Infant group	Total number	Number using penicillin	Expected number from	Number using sulfa	Expected number from
			total mat		*total mat*
Major malformation	194	5	5 0	4	6 9
Controls to major malformation	194	7	5 0	3	6 9
Dead but not malformed	93	4	2 4	2	3 3
Controls to dead but not malformed	93	6	2 4	2	3 3
Dead and/or major malformation	287	9	7 3	6	10 3
All controls	287	13	7 3	5	10 3
Specific malformation types			*all controls*		*all controls*
C N S malformation	11	0	0 5	0	0 ?
Cleft lip and/or palate	10	0	0 5	0	0 ?
Cong heart malformation± other malformation	35	0	1 6	0	0 6
Hypospadias	15	3	0 7	1	0 3
Cong dysplasia of hip	37	1	1 7	0	0 6
Multiple malformation	10	1	0 5	1	0 ?
Mb Down	10	0	0 5	0	0 ?



„ 3 Percentage of women reporting use of analgesic gs during different months of pregnancy according to gnancy outcome —=miscarriage =induced rtion =living infant – =dead infant

2 *Analgesic drugs*

algesic drugs—mainly preparations containing tyl salicylic acid—are used freely during preg ncy as is seen in Fig 3 Already during the first tational month—before the first missed riod—women who will later have a living child a lower consumption than women who will have pontaneous abortion a stillbirth or an induced rtion χ^2 analysis for heterogeneity between se groups gives $\chi^2=10\ 4$ at 3 d f $0\ 02>P>0\ 01$ e small number of women who end with a still th (68) makes it impossible to decide if they be g to the same group as women who have a living ld or to the group of women who will miscarry the subsequent months of gestation the graph of alg sic takers who will have a live birth and those o will have a stillbirth follow each other ll—only during the fourth month is there a differ e but this is not statistically significant ($\chi^2=2\ 5$ l d f N S) The graph based on women who l later have a miscarriage shows a marked rise mpared with that based on women who will have hild The latter shows a maximum in the second nth but the former continues to rise The graph based on women who will have an induced abortion follows that for women who will have a spontane ous abortion during the first three months but then turns downwards abruptly

As is visible from Fig 4 there is no clear-cut difference in analgesic use among women who will have infants of different types normal infants in fants with minor malformation or with major malformations There is a tendency for the graph based on women who will have infants with minor malformations to be slightly elevated especially during the third and fourth month This difference is however of liminal significance (χ^2 for heterogeneity between these three groups during the fourth month gives $\chi^2=6\ 1$ at 2 d f $P\sim0\ 05$) A slightly increased incidence of analgesic use among women with an unwanted pregnancy is found —32 4% against 29 8% among women with a wanted pregnancy—but this is not statistically significant ($\chi^2=2\ 89$ N S) Women married at L M P use analgesics slightly more often than women not married at L M P (32 1 against 29 8% $\chi^2=3\ 4$ N S) These differences resemble but are not as strong as those found for psychopharmaca The mean age of women using analgesics is some what elevated (26 83 years against 26 21 for non users $t=2\ 95$ $0\ 01>P>0\ 001$) again a trend similar to that found for psychopharmaca

Table II compares the use of acetyl salicylic acid (with the possible addition of caffeine or codeine

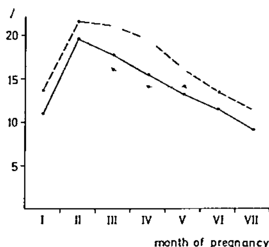


Fig 4 Percentage of women reporting use of analgesic drugs during different months of pregnancy Comparison between normal infants (—) infants with minor ( ) or major ( ) malformations

Table II Number of women using salicylates during the first trimester

Infants with major malformations and matched controls infants without major malformations but dead *within* one year with matched controls

Infant group	Total number	No using salicylates	
Major malformation	194	34	
Controls to major malformation	194	33	
Dead but not malformed	93	12	
Controls to dead but not malformed	93	23	
Dead and/or malformed	287	46	
All controls	287	56	
Specific malformation types			*Expected no from all controls*
C N S malformation	11	2	2
Cleft lip and/or palate	10	1	2
Cong heart malformation± other malformation	35	7	7
Hypospadias	15	2	3
Cong dysplasia of hip	37	7	7
Multiple malformation	10	0	2
Mb Down	10	2	2

and the outcome of *pregnancy* No signs of embryotoxic or teratogenic effect can be found —*there is even a lower incidence of drug use in the group of women who will have an infant dead within one year than in the other groups* According to Table III there is no definite difference in the length of pregnancy if the woman used a[illegible] during any trimester or not There is [illegible] trend in the group that only used such drugs d[illegible] the 2nd–3rd trimester when compared with the group that did not use analgesic drugs at all [illegible] a surplus of prolonged and a slight deficiency of premature pregnancies with a male infant When these two groups are compared with a χ^2-test for trend (12) a possibly significant difference is found $\chi^2 = 4\,9$ at 1 d f $0\,05 > P > 0\,0$[illegible]

Table IV shows that there is no difference with respect to birth weight

A special study was performed on women who had used phenylbutazone or oxyphenbutazone—[illegible] women were found that had used one of these drugs during the first trimester Among these one had a miscarriage six had infants with minor malformations and one had an infant with a major malformation

3 *Iron and vitamin preparations*

The use of iron and/or vitamin preparations [illegible] shown in Fig 5 Women who will have an induced abortion show a markedly lower usag than the others Also women who will have a miscarriage show a reduced intake of such drugs—especially during the later part of the pregnancy period In[illegible]terestingly enough there is also from the [illegible] month onward a reduced intake in women who [illegible] prove to have a dead child A very faint simil[illegible]

Table III *Duration of pregnancy when analgesic drugs were used during the first trimester during the second or third but not the first trimester and when such drugs were not used at all*

Expected numbers (calculated for each sex separately) given within brackets for pregnancies shorter or longer than [illegible] weeks

	Total number	Duration of pregnancy: Less than 38 weeks	38–42 weeks	More than 42 weeks	χ^2 (4 d f)
Boys					
Drug first trimester	654	48 (50)	579	27 (27)	6 [illegible]1 N S
Drug 2nd–3rd trimester	645	43 (49)	566	36 (27)	
No drug	1 090	90 (83)	963	37 (46)	
Girls					
Drug first trimester	696	54 (54)	618	24 ([illegible])	0 48 N S
Drug 2nd–3rd trimester	644	46 (50)	578	20 (21)	
No drug	1 037	83 (80)	9[illegible]1	33 (34)	

χ^2 between drug groups within sexes = 6 69 N S at 8 d f

ble IV Birth weight in non malformed infants when the woman had or had not used analgesic drugs ing the first trimester during the second or third but not the first trimester and not at all

	Total number	Birth weight kg						χ^2 (10 d f)
		<2.5	2 5–3	3–3 5	3 5–4	4–4 5	>4 5	
g first trimester	654	19	78	201	228	106	22	8 36 N S
g 2nd–3rd trimester	645	22	60	214	230	100	19	
drug	1 090	48	111	365	384	155	27	
g first trimester	696	33	105	264	270	6?	12	3 09 N S
g 2nd–3rd trimester	644	29	100	253	198	50	14	
drug	1 037	42	173	411	313	79	19	

etween drug groups within sexes = 11 45 at 20 d f N S

s visible also for women who will later on e a child with a major malformation (Fig 6) and ese two groups are added (perinatal pathol) and compared with the group of women who have a living normal child the difference is ous During the seventh month 59% of the ter women and 67% of the latter use iron and/or min preparations (χ^2=5 5 0 02>P>0 01)

he use of iron and vitamin preparations during y pregnancy is thus similar irrespective of the come of the pregnancy—the only exception be induced abortions The mean age of women g such drugs is slightly higher than the mean age women not using these drugs but the difference ot significant (26 6 and 26 3 years resp t=1 5) The acceptability of the pregnancy and the l status of the women at L M P influence the of these drugs markedly Among women with a ted pregnancy 38 7% use these drugs during first trimester against 28 0% among women an unwanted pregnancy (χ^2=44 3 P<0 001) responding figures for women married at P and not married at L M P are 40 5 and % respectively (χ^2=52 5 P<0 001)

fter th first trimester virtually all women re ing a wanted pregnancy have used iron and/or mins but only 74% of women who have an anted pregnancy—the same difference is seen women married at L M P (near 100%) and not ried at L M P (87%) The mean age of women g these drugs after the first trimester is 26 39 rs—nearly identical with that of all women in led 26 37 years

able V compares the duration of pregnancy when iron vitamin preparations had been used (any trimester) or had not been used There is a highly significant difference between the two groups mainly due to differences in the incidence of preg nancies lasting less than 38 weeks In Fig 7 this group is broken down further It appears that the presence or absence of other drugs besides the iron vitamin preparations has little significance for the incidence of pregnancies of less than 38 weeks

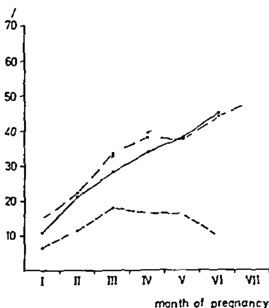


Fig 5 Percentage of women using iron and/or vitamin preparations during different months of pregnancy according to pregnancy outcome —= miscarriage -= induced abortion = living infant — = dead infant.

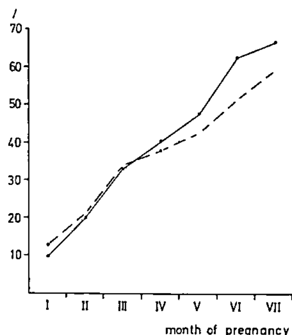


Fig 6 Percentage of women using iron and/or vitamin preparations during different months of pregnancy Comparison between living normal infants (—) infants with major malformations ( ) and with infants with perinatal pathology (i e stillbirth and/or major malformation) (–)

In Table VI birth weights are compared for normal infants born to women who used or did not use iron vitamin preparations and with a gestational length of 38–42 weeks For boys a significant difference is found with an excess of low birth weight infants in the group that did not take iron vitamins during pregnancy and a similar trend is seen also for girls Fig 8 illustrates this phenomenon

DISCUSSION

No definite teratogenic effect has been demonstrated with penicillin or sulphonamide which agrees with the general view on the subject (18) We have demonstrated however that women who will later have a miscarriage use antibiotics or sulphonamides more frequently than women whose pregnancies will go to term with certainty during the second gestational month but probably also during the first A reasonable explanation would be that these drugs have been prescribed for infectious diseases which themselves may cause miscarriage. The high incidence of infectious diseases—and therefore also of antibiotic use—during the second pregnancy month may be related to the high F levels during that part of the pregnancy (?) as it has been claimed that HCG during pregnancy can have an immunological function and reduce maternal defence against infection

Relatively few women used penicillin during the first trimester Among 5 002 women that gave birth to an infant 128 report the use of penicillin—4 of these had infants with major malformations which is just the expected number The recorded figure of could however be a random underestimate of a true number of 10 ($P=0$ 05) and therefore the recorded lack of teratogenicity could hide a doubling in malformation incidence There are no facts indicating that this would be the case—the only observation is perhaps that three of the five infants had hypospadias It is hardly likely that penicillin could cause hypospadias but it may be used to treat a relevant infection This is mere speculation however

Table V *Duration of pregnancy when iron vitamin preparations were or were not used during pregnancy (any trimester)*

Expected numbers (calculated for each sex separately) given within brackets for pregnancies shorter or longer than 42 weeks

	Total number	Duration of pregnancy: Less than 38 weeks	38–42 weeks	More than 42 wekeks	χ^2 (2 d f)
Boys					
Drug	1 878	123 (142)	1 674	81 (79)	
No drug	511	58 (39)	434	17 (21)	12 2
Girls					
Drug	1 935	109 (131)	1 761	65 (63)	
No drug	442	52 (30)	378	12 (14)	21 6

0 01>P>0 001   * P<0 001

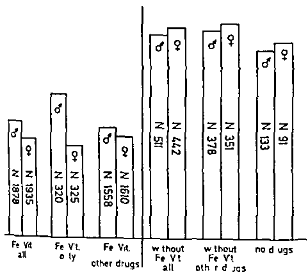


Fig 7 Percentage of infants born before the 38th gestational week according to drug use during pregnancy (any trimester) Fe Vit=iron and/or vitamin preparations N gives number of women in each group

e pattern of analgesic use apparent in this shows trends resembling those found for otropic drugs (8) There is already a higher of analgesics during the first gestational h among women who will later on have a mis age It is common experience that analgesics often used instead of psychopharmaca by en In women who will have a miscarriage is a steady increase in use of analgesics espe during months five and seven This may fol vaginal bleeding and other complications d to the abortion

ere is little difference in the use of analgesics in en who will have a malformed child and in en who will have a normal child but there is a t in ease in an lgesic use during the third month among women who will later on have a child with minor malformations—but not with major Richards (13) stated that a significantly increased use of analgesics was found during the first trimes ter among women who will have a malformed child However his data was obtained by retrospective questioning So for instance strong and significant correlation between birth of malformed children and unbalanced or doubtful diet was found Such findings probably suggest bias in the collec tion of data and not real differences Crombie et al (4) on the contrary found a slightly lower con sumption of analgesics among women who had a malformed child than among women who had a normal child Interestingly enough Nelson & Forfar (12) also found an increased use of analgesics

e VI *Birth weight in non malformed infants when the woman had or had not taken iron vitamin arations during pregnancy (any trimester)*
tional length 38–4? weeks

	Total number	Birth weight kg						χ^2 (5 d f)
		<2 5	2 5–3	3–3 5	3 5–4	4–4 5	>4 5	
	1 674	25	139	565	612	275	58	13 5 ( )
rug	434	14	40	138	176	59	7	
	1 761	36	258	709	562	159	37	5 8 N S
rug	378	13	56	149	129	25	6	

etween groups within sexes=19 3 at 10 d f 0 05>P>0 025
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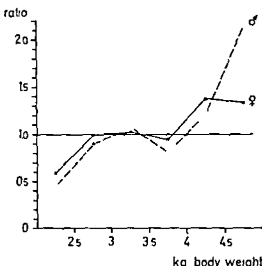


Fig 8 Ratio showing the percentage of infants within each weight class whose mothers used iron and/or vitamin preparations divided with the percentage of infants whose mothers did not use such drugs Ratios below 1 thus indicate that the former group is underrepresented ratios above 1 that the latter group is so —=boys =girls

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ım preparations is probably mainly an indica f prenatal maternal care and other social con is which may be of importance (cf 1) Thus ing habits and nutritional factors could be cor ed with the use of these drugs The observa illustrate that great care has to be taken when lusions are drawn on drug effects on embry or fetal development from mere statistical dence A similar situation occurs with anti tic drugs and their protective effects against carriage as discussed by us in a previous pa 9)

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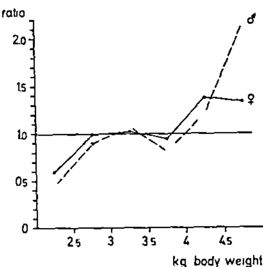


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Acta Obstet Gynecol Scand 55 297–304 1976

HISTAMINE METABOLISM DURING THE MENSTRUAL CYCLE

F Jonassen G Granerus and H Wetterqvist

From the Department of Obstetrics and Gynecology (Head Prof N Wiqvist) the Department of Clinical Physiology I (Head Prof A Carlsten) and the Department of Clinical Chemistry (Head Prof S Lindstedt) Sahlgren s Hospital University of Goteborg Sweden

The urinary excretion of histamine and its ...ites methylhistamine (MeHi) and methylimidazo- ...acid (MeImAA) was measured during the men... ...ycle in nine healthy women one allergic woman ...e non pregnant women with anovulatory regular ... Simultaneous urinary analyses of luteinizing ...e (LH) and total estrogens were performed The ...women showed individual variations in the excre... ...histamine MeHi and MeImAA This observation ...n interpreted as an expression of minor individual ...ces in the catabolism of histamine At midcycle an ... in the urinary excretion of histamine metabolites ...netimes evident and a statistically significant corre... ...ould be established between MeHi and estrogen in ... These results may support previous findings of ...ne release by estrogens in uterine tissue but may ...lect an elevated histamine formation The allergic ... excreted constantly increased amounts of hista... ...nd its metabolites especially when her allergic ...ms became aggravated pre menstrually She did ...ibit any change in MeImAA excretion at midcycle ... MeHi-excretion varied with the excretion of estro... ...n the urine The subjects with anovulatory men... ...cycles had low values of histamine and metabolites ...h within the normal variations

INTRODUCTION

...al experiments indicate that several endocrine ...s affect the metabolism of histamine Sex dif... ...ces in histamine turnover have been found in ...t (32 33 34) and in the mouse (26 35) the ...es excreting more unmetabolized histamine in ...urine than the males During pregnancy a ...ed elevation in histamine formation is found ...arly in these animals and in the hamster (27) ...evidence of hormonal influences on histamine ...bolism in man is only fragmentary In human ...an y increased histamine excretion has been ...ted by several authors (2 6 7) and recently a ... increase in the excretion of the histamine metabolites methylhistamine (MeHi) and 1 methyl-4-imidazoleacetic acid (MeImAA) (7) was also demonstrated No difference has been found between men and women in the urinary excretion of histamine and its metabolites (5 10) However even under standardized dietary conditions there was a wide range in the amount of MeHi excreted by the females (10) The lowest value was found in a woman using oral contraceptives and the highest in a woman during menstruation The range in MeHi excretion was considerably narrower in human males In two women receiving follicle stimulating hormone (FSH) and human chorionic gonadotrophin (HCG) a correlation seemed to exist between the ratio of MeHi to histamine in urine and the urinary excretion of estrogens (11) The aim of the present investigation was to study the histamine metabolism more extensively during the menstrual cycle Special attention was given to the excretion of histamine and metabolites in the pre and post ovulatory phases and at the time of the LH peak in order to evaluate any possible relationship to the hormonal variations during the menstrual cycle

MATERIAL AND METHODS

Altogether thirteen cycles were examined in ten ovulating women Nine of these women were apparently healthy but one woman had a mild allergic skin disease For comparison three anovulatory but regular cycles were examined in three healthy non pregnant women Pertinent data on these thirteen women are given in Table I

During each menstrual cycle urine was collected on as many days as practically possible The urine was collected in 24-hour portions and immediately placed in a refrigerator at +4 C Samples for hormone analyses were withdrawn and the urine was then mixed with hydrochloric acid (1 M) to give a pH below 1 On the days of urine

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Table I *Pertinent data on the subjects*

Subject	Age (y)	Parity	Weight (kg)	Smoking cigarettes/day
A	22	0	54	0
B	22	0	56	>10
C	23	0	82	<10
D	26	1	54	0
E	26	1	58	0
F	46	0	57	0
G	47	1	58	0
H	51	0	74	0
I	53	3	60	0
J	32	1	64	>10
K	26	1	58	0
L	28	0	55	>10
M	49	0	59	0

collection the subjects were given a standardized diet as described by Granerus (10)

Analyses of histamine and metabolites

Histamine (Hi) in the urine was determined by a bio-assay technique according to Wetterqvist & White (36) The values were corrected for recovery and expressed as μg histamine base excreted per 24 hours The identity of histamine was established in accordance with the method of Reuse (25)

Methylhistamine (MeHi) in the urine was determined according to Fram & Green (5) White (38) and Granerus et al (9) The values were corrected for recovery and expressed as μg base excreted per 24 hours

1 methyl-4-imidazoleacetic acid (MeImAA) was determined by a method described by Granerus & Magnusson (8) with slight modifications (10) In addition a technique with an internal standard was introduced to increase the sensitivity of the method A minute amount of ^{14}C labelled MeImAA was added to the urine sample After the finishing thin layer chromatography the whole material obtained from the cellulose column separation was evaporated to dryness and then dissolved in 1 2 ml aq dest One was mixed with 10 ml Instagel (Packard) and the radioactivity measured in a Packard Tri Carb scintillation counter The quenching effect was estimated in each sample by addition of 50 μl ^{14}C toluol (4 15×10⁵ dpm/ml) and recounted The recovery of ^{14}C toluol was 92%±3 8% (mean ±S D) and the corrected recovery of added ^{14}C MeImAA was 80% ±6 9% (mean ±S D) By this technique each analysis of MeImAA could be corrected for the losses in the whole analytical procedure and the values were given as mg per 24 hours ^{14}C MeImAA was obtained by incubation of ^{14}C histamine (The Radiochemical Center Amersham) and carrier MeImAA with cat liver The final isolation of ^{14}C MeImAA was performed by ion exchange chromatography (1)

Hormone analyses

Luteinizing hormone (LH) was determined by a radioimmunosorbent technique according to Wide et al (37) The values are expressed in I U per 24 hours in urine and ng per ml in serum

The total excretion of estrogens in urine was [illegible] according to the method of Brown (3) and [illegible] the values are expressed in μg per 24 hours

Analysis of plasma progesterone was performed as described by Johansson (15) with the modifications suggested by Ellingboe et al (4)

The analyses of estrogens and progesterone were carried out at the Department of Clinical Chem[illegible] Sahlgren s Hospital

Definition of the day of ovulation

In order to verify the day of ovulation the LH peak [illegible] urine and the following rise in plasma progesterone [illegible] determined According to Johansson & Wide (16) [illegible] Yussman & Taymore (39) and others ovulation [illegible] the day after the LH peak An increase of progesterone [illegible] plasma after the LH peak was additional evidence of ovulation (15 16 23)

Statistical methods

Conventional statistical methods were used for the calculation of means and standard error of means A traditional correlation analysis based on pairs of observations [illegible] from each subject—suffer the weakness of [illegible] intraindividual correlations with interindividual correlations With the present method of performance of [illegible] experiments i e longitudinal studies in a few individuals the individual correlation only can be obtained [illegible] product moment correlation coefficient of estrogen [illegible] MeHi was calculated for one cycle for each woman [illegible] subject C the first cycle and in subject J the second [illegible] By using the correlation coefficients as a sample the [illegible] tive correlation between estrogen and MeHi was [illegible] tablished (two sided tests) by a non-parametric test [illegible]

RESULTS AND COMMENTS

Ovulatory cycles

Table II gives the mean value S E and range [illegible] the urinary excretion of histamine and metabolites in each ovulatory cycle studied In some of [illegible] healthy subjects there are relatively high [illegible] ues of histamine and MeHi but it is also evident from Table II that the standard error of the mean [illegible] mostly of the same magnitude for each component This indicates that different women may have significantly different excretion values of histamine and MeHi Such an interindividual variation [illegible] exemplified by subjects A B and D who rather constantly had a higher urinary excretion of [illegible]

Fig 1 Urinary excretion of luteinizing hormone (LH) estrogen (Estr) histamine base (Hi) methylhistamine (MeHi) and 1 methyl-4-imidazoleacetic acid (MeImAA) [illegible] four ovulating women (A B D and G in Table I) [illegible] one menstrual cycle

ble II *Average daily urinary excretion of tamine base (Hi) and methylhistamine (MeHi) in per 24 hrs and 1 methyl-4 imidazoleacetic acid lmAA) in mg per 24 hrs during one two or e menstrual cycles in nine healthy ovulating men and one allergic ovulating woman (J)*

	Compound	No of samples	Mean ±S E	Range
	Hi	15	35±4	21–79
	MeHi	15	18 ±9	1?2–?47
	MeImAA	16	2 63±0 12	1 60–3 40
	Hi	9	60±4	39–74
	MeHi	9	214±9	184–261
	M ImAA	9	3 33±0 44	2 30–6 50
	Hi	1?	22±?	14–?8
	MeHi	1?	271±_2	167–409
	Hi	11	23±3	13–43
	MeHi	11	?61±13	211–331
	Hi	11	48±5	24–77
	MeHi	11	119±12	71–206
	MeImAA	11	3 ?1±0 2?	2 _0–4 50
	Hi	8	25±3	15–36
	MeHi	8	137±12	99–?04
	Hi	13	16±1	1?–19
	MeHi	13	184±7	137–?44
	Hi	1?	16±2	8–31
	MeHi	1?	134±8	101–177
	MeImAA	1?	3 06±0 18	2 40–4 ?0
	Hi	8	15±1	1?–?1
	MeHi	8	170±7	145–?02
	Hi	11	20±3	1?–39
	MeHi	11	117±15	65–233
	Hi	9	31±3	??–46
Y	MeHi	9	470±48	268–556
	Hi	1?	46±5	20–67
	MeHi	1?	479±34	299–660
	MeImAA	1?	4 96±0 35	4 20–8 40
	Hi	8	50±9	21–107
	MeHi	1	401± 6	279–625
	MeImAA	1?	3 56±0 0	2 70–5 10

...ulatory cycles

...urinary excretion of histamine and metabolites ...three women with anovulatory cycles is pre...ted in Table III The mean values for histamine ...MeHi are in the lower range of what is found in ...ovulatory cycles The excretion of total estro... was also somewhat lower The third case (sub... M) was near the menopause as shown by high ... values but this did not seem to have any effect ...the histamine metabolism as judged from the ...paratively low urinary excretion of histamine ...MeHi and MeImAA (*Fig 3*) In the other two wom-

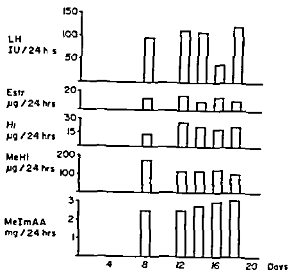


Fig 3 Urinary excretion of luteinizing hormone (LH) estrogen (Estr) histamine base (Hi) methylhistamine base (MeHi) and 1 methyl-4-imidazoleacetic acid (MeImAA) in a woman (M in Table I) during an anovulatory cycle

en MeImAA was determined only in a few urinary samples at midcycle which yielded comparatively low values

DISCUSSION

In man histamine is mainly inactivated by methylation in the imidazole ring and subsequent oxidative deamination the intermediate metabolite being MeHi and the final metabolite MeImAA MeImAA

Table III *Average daily urinary excretion of histamine base (Hi) and methylhistamine base (MeHi) in µg per 24 hrs in three healthy non pregnant women during one spontaneous anovulatory cycle In subject M (Table I) the urinary excretion of 1 methyl-4 imidazole acetic acid (MeImAA) in mg per 24 hrs was also measured*

Subject	Compound	No of samples	Mean ±S E	Range
K	Hi	10	29±3	17–39
	MeHi	10	118±11	60–160
L	Hi	11	8±1	7–1?
	MeHi	11	113±12	50–180
M	Hi	5	21±2	13–27
	MeHi	5	124±13	100–180
	MeImAA	5	2 78±0 1?	2 50–3 10

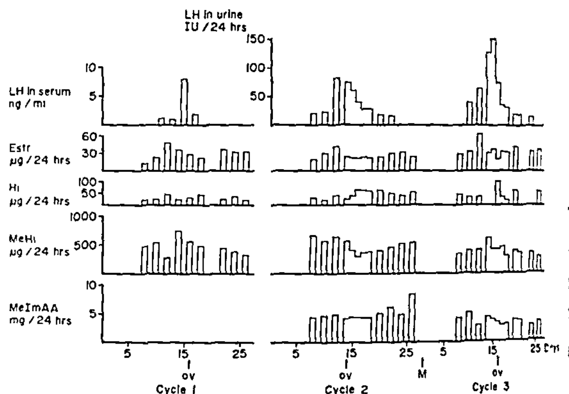


Fig 2 Urinary excretion of luteinizing hormone (LH) estrogen (Estr) histamine base (Hi) methylhistamine base (MeHi) and 1 methyl-4 imidazoleacetic acid (MeImAA) in an allergic ovulating woman (J in Tab [illegible]) during three menstrual cycles During the first cycle [illegible] was measured in serum instead of urine

lized histamine than any of the other six healthy women Another example is subject C who excreted small amounts of histamine but had a constantly high excretion of MeHi This subject was studied during a second menstrual cycle in which she had mean values of histamine and MeHi of the same magnitude as those in the preceding cycle

The mean value of the quantitatively dominating histamine metabolite MeImAA was about the same in the four healthy women studied (A B D G)

Fig 1 shows the daily urinary excretion of histamine MeHi MeImAA LH and total estrogens in four of the healthy subjects (A B D and G) during several days of one menstrual cycle It will be seen that there are no obvious differences in the excretion of histamine and metabolites in the pre-ovulatory period compared to the post-ovulatory period However there was a tendency to an increase in the urinary excretion of MeImAA at midcycle in at least two of the subjects In subjects D and G the histamine excretion tended to parallel the MeImAA excretion whereas this trend was less evident for the MeHi values

The complete data from three menstrual cycles in the allergic woman (subject J) are given in Fig [illegible] The excretion values of histamine and meth[illegible] were about doubled in this woman as compar[illegible] the healthy women (Table II) During the first a[illegible] last menstrual cycle studied she had no sym[illegible] but during the second cycle she felt slight [illegible] the skin of her hands and arms being mo[illegible] nounced in the premenstrual phase The appea[illegible] ance of these symptoms coincided with a mark[illegible] increase in MeImAA (day 76) No chan[illegible] MeImAA excretion was found in this wom[illegible] midcycle although the MeHi values show[illegible] tendency to increase just before ovulation a[illegible] crease afterwards i e paralleling the variat[illegible] urinary estrogens Determination of M[illegible] not carried out in cases C E F I and H due to [illegible] of laboratory resources However MeHi was d[illegible] termined in all subjects By using the correla[illegible] coefficients as a sample a positive correlation b[illegible] tween the urinary excretion of estrogen and M[illegible] in subjects A–J was obtained at the [illegible] level [illegible] sided tests) by a non parametric test [illegible] correlation was found between estrogen and h[illegible] mine nor between LH and MeHi or h[illegible]

ila.ory volunteers had a constantly increased :amine turn-over In clinical practice an increase ymptoms in allergic subjects is often observed before menstruation This corresponds with the ervation in the allergic woman of the present estigation and suggests an increase in histamine abolism.

t has been shown that in healthy women the retion of histamine metabolites varies during the strual cycle and seems to fluctuate with the ogen levels As far as we know this is the first ort demonstrating a possible connection be en histamine metabolism and a normal physio- cal process in man Further studies may eluci whether estrogens trigger a release of hista e or induce an increased histamine formation

ACKNOWLEDGEMENTS

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is quantitatively by far the most important histamine metabolite excreted in the urine and therefore the best measure of the total histamine turnover in the body However in order to obtain reliable information about the endogenously liberated histamine it is absolutely necessary to minimize contamination of exogenous histamine by keeping the subjects studied on a standardized diet with a low histamine content (10) All subjects in this study were kept on such a diet each day of urine collection Under standardized dietary conditions the urinary excretion of MeImAA is rather constant in healthy human subjects and has been reported to be 2 3±0 3 and 2 4±0 5 mg per 24 hours (mean ±S E) in two different series of non smoking cases (10 19) The values are somewhat higher among cigarette smokers (10 31) The mean values of MeImAA found in the present study agree with the results of these reports except in the allergic woman who had higher values

The mean values of histamine and MeHi also correspond to earlier reports in healthy human subjects with standardized diet (5 10) but there were some interesting exceptions Three of the nine healthy women had a constantly higher output of unmetabolized histamine and another healthy woman with low urinary excretion of histamine had constantly high excretion of MeHi These findings have been interpreted as signs of minor individual differences in the catabolism of histamine in the body Catabolic studies with ^{14}C histamine in man have shown a very rigid catabolic pattern of injected histamine in normal as well as in pathological states but this fact does not exclude the occurrence of individual differences as found in the present study (20) The exceptions illustrate the difficulties in evaluating any changes in histamine metabolism from isolated individual observations of histamine and MeHi without standardization of experimental conditions

It has previously been shown that estrogens rapidly release histamine from uterine tissues in various species including man and that LH releases ovarian histamine in the rat (29) A role for histamine as a mediator of the hormonal vascular effects on these organs has been proposed by Szego (29) The results of the present investigation indicate the occurrence of an increase in urinary excretion of histamine metabolites at midcycle especially MeImAA A probably significant positive correlation between the urinary excretion of estrogens and MeHi was also found verifying the results reported by Green et al (11) No correlation was found between LH and histamine metabolites

In the rat rapid restoring of the histamine content in the uterus occurs within 14 hours after a [illegible] injection of estradiol 17 β (28 29) Histidine decarboxylase activity has been demonstrated in the [illegible] uterus (18) According to Szego (29) variation [illegible] endogenous estrogen levels during the estrous cycle of the intact rat was reflected in the a[illegible] inverse relation of uterine histamine concentration Marshall studied the cycles and found a small [illegible]crease in histamine excretion at estrous as well after administration of stilboestrol but this might [illegible] explained by a concurrent depression of urine volume at estrous and during treatment with estrogen (21) By measuring both histamine and MeHi in [illegible] urine during inhibition of diamine oxidase [illegible] & Wetterqvist found no changes in histamine turnover at estrus (to be published)

According to Iversen (14) estrogen treatment [illegible]creases the number of mast cells in the human cer[illegible]vix and in the myometrium of guinea pigs [illegible] basophil cells in blood also decrease in [illegible] at midcycle which may reflect an estrogen ef[illegible] (22 30)

In mice estrogens primarily increase histamine formation Injections of estradiol in female [illegible] cause a gradual and long lasting increase in [illegible] histamine due to a greatly elevated histamine [illegible] ming capacity of the mouse kidney (1[illegible] 27) During pregnancy some species also show a con[illegible] increase in histamine formation (18 27) In [illegible] however only a small increase in histamine [illegible] over occurs during pregnancy (? 6 7) In the present investigation there was evidence of an [illegible] in histamine metabolism in connection with [illegible] tion which might indicate an effect of estrogen [illegible] histamine formation or liberation in the [illegible] body It is a well known fact that estrogens exert [illegible] selective growth effect upon all the female sex [illegible] gans The importance of histamine as a growth factor has been discussed most thoroughly by Ka[illegible] son et al (18)

It is of interest to note that subjects with [illegible] anovulatory cycles and low estrogen values had [illegible] normal excretion values of histamine and metabolites However the anovulatory cases were [illegible] to allow statistical analysis of the data

The allergic woman who had higher and [illegible] fluctuating estrogen values in urine than the [illegible]

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EPIDURAL ANALGESIA IN LABOUR

IV *Influence on Uterine Activity and Fetal Heart Rate*

N Raabe and P Belfrage

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tract The influence of epidural block with bupiva e (Marcaine adrenalin®) on fetal heart rate uterine vity and the frequency and intensity of contractions studied in twenty-five nulliparae at term Uterine vty was found to decrease during the first 30 minutes wing epidural block In the time interval 30 to 40 s after epidural block uterine activity increased and attained the same level as during the last 10 tes before analgesia The frequency of uterine con tions did not decrease after the block The lower s of uterine contractility were due only to a lower itude of the contractions The regularizing effect of ural analgesia on incoordinate uterine action was d The recording of fetal heart rate in the time interval ied revealed no pathological findings Mode of de ry mean labour duration and Apgar scores after ural block were comparable with earlier studies of a er patient population This study suggest that epidural lgesia does not induce any important changes in fetal rt rate but temporarily decreases uterine activity

tinuous lumbar epidural analgesia during labour h bupivacaine as a local analgesic agent has been d since 1969 at the department of obstetrics and ecology Karolinska Hospital Stockholm This dy of 25 deliveries under epidural block was ertaken to evaluate the influence of epidural ck with a long acting local analgesic upon uterine vity and fetal heart rate

MATERIAL AND METHODS

Pa ts

nty-five healthy nulliparous women in established our at 37–41 weeks gestation calculated from the date the last menstrual period were selected for this in tigation. The age of the patients ranged between 18 and years (mean 23 9 years) All mothers had uncomplicated pregnancies All babies were singleton and delivered by vertex presentation

Epidural analgesia

The analgesia was started at a cervical dilatation of approximately 4–5 cm Lumbar epidural block was performed in a conventional way according to a technique described earlier (13 20) Bupivacaine 0 25% with epinephrine 1 200000 (Marcaine adrenaline®) was used as the analgesic agent After an initial test dose of 2 ml 8 ml were administered through the catheter into the epidural space This dose was then repeated every second hour until delivery

Data aquisition

At a cervical dilatation of 4–5 cm after membrane rupture a scalp electrode was applied to the head of the fetus Simultaneously an open-ended polyethylene catheter filled with sterile water was inserted transcervically into the uterine cavity and connected to a calibrated transducer (HP 1280B/C) for evaluating intrauterine pressure

For recording the fetal heart rate (FHR) a Hewlett Packard cardiotocograph (HP 8020 A) and a Ruttgers Spiral Scalp Electrode (16) (HP 15130 A) was used

Fetal blood sampling (FBS) from the scalp was collected according to the method of Saling (18) and the pH was determined on a Radiometer instrument consisting of the blood microsystem BMS 3 and the pH Meter 71

Definitions

Intensity (amplitude) of each contraction is defined as the amount of rise in amniotic pressure above the resting uterine tonus Frequency is expressed as the number of contractions per 10 minutes calculated from the time interval between peaks of contractions Uterine activity in Montevideo units (MU) is the product of the intensity of the contractions (in mmHg) multiplied by their frequency and is expressed in mmHg per 10 minutes Uterine tonus is defined as the lowest pressure between successive contractions (11) For evaluating the FHR changes the nomenclature of Hammacher (4) and Hon (6) was used Changes in FHR patterns in association with fetal blood sampling were excluded

Table I *Clinical data of patients in study*

Patient no	Age	Labour duration after block (minutes)	Oxytocin stimulation[b]	Delivery	Apgar score 1 min	5 min	10 min	Weight of infant (g)
1	26	256	–	VE	3	8	10	3 460
2	22	280	+	VE	10	10	10	4 400
3	26	235	–	VE	6	8	10	3 150
4	24	139	–	VE	6	10	10	3 550
5	22	54	–	PN	10	10	10	[illegible]810
6	26	254	–	PN	10	10	10	3 [illegible]60
7	25	79	–	PN	10	10	10	[illegible]970
8	20	64	–	PN	10	10	10	2 570
9	30	800	+	PN	9	10	10	3 350
10	18	118	–	PN	9	10	10	[illegible]750
11	26	567	+	VE	10	10	10	3 220
12	23	297	–	PN	9	10	10	3 420
13	23	250	–	PN	10	10	10	3 600
14	26	254	–	PN	10	10	10	4 370
15	23	141	–	PN	9	10	10	3 380
16	23	275	+	PN	9	10	10	3 410
17	24	145	–	VE	3	5	6	3 3[illegible]5
18	26	281	+	VE	8	10	10	3 020
19	21	232	+	PN	9	10	10	3 550
20	20	115[a]	–	CS	9	10	10	3 650
21	30	397[a]	–	CS	9	10	10	[illegible]500
22	18	313	+	VE	10	10	10	3 820
23	26	375	+	PN	6	9	10	3 000
24	23	240	+	PN	9	9	10	3 490
25	26	494	+	VE	4	9	10	3 000
$\bar{x}$	23 9	267 1						3 33[illegible] 0
S D	3 1	170 0						470 9
n	25	23						25

[a] Excluded in mean value of labour duration after block
[b] Oxytocin stimulation always was started more than 40 min after epidural block

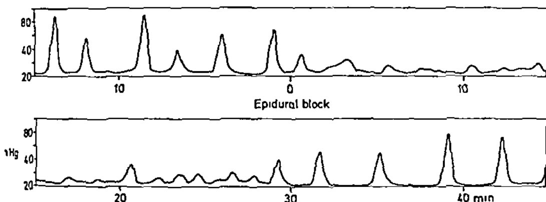
RESULTS

Uterine activity and frequency

The clinical data are presented in Table I Uterine activity was found to decrease during the first 30 min following epidural block (Table II and Fig 1) This difference is significant (0 01>p>0 001) In the time interval 30 to 40 min after epidural block the uterine activity increased again and att[illegible] same level as during the last 10 min before [illegible] gesia Uterine activity also decreased imme[illegible] before analgesia was given There was even a [illegible] nificant difference in uterine activity 10 to 20 [illegible] before the block compared with the last 10 m[illegible] fore analgesia (0 01>p>0 001)

Table II *Intensity (I) in mmHg frequency (F) in contractions/10 minutes and uterine activity in [illegible] video units (MU) before and after epidural block*

	Before epidural block									After epidural block					
	−30 min			−20 min			−10 min			+10 min			+[illegible]0 min		
	I	F	MU	I	F	MU	I	F	MU	I	F	MU	I	F	M[illegible]
Mean	34 3	3 7	128 6	32 5	3 7	120 5	27 9	3 6	104 5	19 5	3 6	73 7	[illegible]0 0	3 6	[illegible]
S D	11 8	0 9	52 7	11 7	1 0	47 2	9 3	0 9	48 7	8 0	1 [illegible]	39 7	9 [illegible]	1 5	[illegible]
S E	2 4	0 2	10 8	2 4	0 2	9 5	1 9	0 2	9 8	1 6	0 3	8 0	1 9	0 3	[illegible]
n	24			25			25			25			25		



I Influence of epidural block with bupivacaine on bur

f the patients are divided into two groups before lgesia one group with uterine activity above MU (13 patients) and the other group with ute activity below 100 MU (12 patients) there will a more moderate decrease *of activity in the first* (mean 149 MU before and 108 MU after 27% decrease) and a more demonstrable de in the second group (mean 84 MU before and MU after block 35% decrease)

he intensity of *uterine contractions will de* ase during the first 30 min after epidural block 01>p) in comparison with the 30 min time peri before epidural block

he frequency of uterine contractions does not rease after the block *Lower levels of uterine* ivity are due only to a lower amplitude of the tractions (Figs 1 and 2)

n two cases incoordinate uterine activity was ed before epidural block After the onset of lgesia the pattern of *uterine contractility became* mal (Fig 3)

n 10 of the 25 cases oxytocin was utilized fol ing the period of observation

Fetal heart rate (FHR) changes

The recording of FHR in the time interval studied (30 min before and 40 min after epidural block) revealed no pathological findings In 6 cases early de

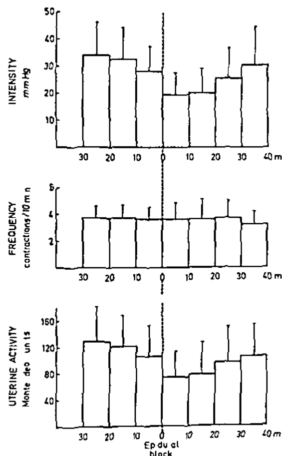


Fig 2 Influence of epidural block with bupivacaine on uterine activity

I

F	MU	+40 min I	F	MU
37	96 4	30 5	3 2	104 9
13	53 3	13 9	1 0	49 1
03	10 7	4 8	0 2	10 2
3			23	

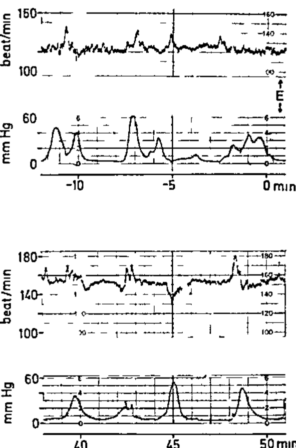


Fig 3 Influence of epidural block with bupivacaine on incoordinated uterine action Epidural block at E

celerations were noted before as well as after epidural block In one case a moderate bradycardia noted before epidural block and throughout ur To evaluate these findings FBS was per med 10 and 30 min after epidural block and at a cervical dilatation of 10 cm The pH was 7 29 7 28 and 7 24 respectively and the baby received an Apgar score of 10 at birth

A temporary decrease of the beat to beat variation of the fetal heart rate was observed in 6 cases In one case an oscillation type O was noted during the 20 min before and the 30 min after the block 40 min after analgesia the oscillation returned to normal (type 2) and the baby was awarded an Apgar score of 9 at one min

Fetal blood sampling

In order to evaluate the bupivacaine concentration in fetal blood (1) fetal scalp blood was obtained by the Saling technique in 7 cases 20 min after analgesia and in 8 cases 10 and 30 min after epidural block

The pH was normal in all cases and ranged between pH 7 27 and 7 42

Delivery and condition of the newborn

Mode of delivery mean labour duration after epidural block and Apgar scores of these 25 cases were comparable with earlier studies of a larger population (13) In one case vacuum extraction was performed because of a severe umbilical cord complication The other vacuum extractions formed due to secondary uterine inertia The indication for caesarean section was in case 20 an umbilical cord complication and in case 21 pelvis

DISCUSSION

The results of this study indicate that there is significant decrease in uterine activity during the initial 30 min after epidural block This is manifested primarily by a reduction of the intensity of the contractions without any change in frequency This phenomenon has been described earlier (5, 17 21) when lidocaine mepivacaine or prilocaine were administered This investigation has clearly shown that this is also the case when bupivacaine is used In addition this study indicates that epidural block will depress the amplitude of uterine contractions when given during the early stage of labour In well established labour the depression of uterine activity is more moderate In both groups oxytocin stimulation will however be corrected Shorter acting drugs such as lidocaine must be given more often and consequently they should influence the duration of labour more than longer acting drugs such as bupivacaine since a temporary decrease of uterine activity is seen after each injection If lidocaine is used a continuous drip infusion might be more convenient (2? 23)

The regularizing effect of epidural analgesia on incoordinate uterine action is well known (9 10 ...) and has been observed also during this study Following epidural block and a period of depressed uterine activity the contractions return to normal even without oxytocin stimulation In practice it can be difficult to stimulate a patient with incoordinate uterine activity without good pain relief and this indication for epidural block is therefore important

The decreasing uterine activity before epidural block is more difficult to evaluate Prior to the block

patient is in the supine position but thereafter the lateral position just before epidural ture This change in position might cause re uterine activity With the technique used in investigation the evaluation of uterine tonus is otally accurate but a pathological rise in tonus he recorded

dic changes of FHR such as early decelera were found in this series This pattern can be idered normal (6 7) No pathological periodic R changes or fetal bradycardia as reported to after paracervical block (15 19) have been rved after epidural block in this study In 6 es a decreased oscillation of FHR was noted epidural analgesia Statistical evaluation of could not be performed due to the vely small number of cases A similar obser has been reported earlier (5 14) and in an er study (2) it was shown that decreased FHR llation was not associated with high fetal bupi levels This pattern is a rather nonspecific i which for example can be elicited by pine pethidine and diazepam (3) Some authors 1? 24) have reported pathological FHR changes epidural block but these findings could be confirmed in the present study A difference dosage or fetal bradycardia due to maternal otension could explain the different findings

his study suggests that epidural analgesia does induce any important changes in fetal heart rate rather effects a temporary decrease in uterine vity In our opinion these findings do not rep any drawback when lumbar epidural block labour is needed for effective pain relief

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SURVEY RADIOGRAPHY OF ABDOMEN FOLLOWING CAESAREAN SECTION WITH PARTICULAR REFERENCE TO CAECAL DIAMETER AND THE PRESENCE OF FREE SUBDIAPHRAGMATIC GAS

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ct The literature concerning perforation and immi erforation of the caecum is reviewed The greatest ance is attached to 5 cases of perforation of the n associated with paralytic ileus following Caesarean 1 The caecal diameter was determined by radio r in 100 patients on the 3rd and 5th day after rean section At the same time the volume of sub agmatic free gas was assessed An average caecal ter of 6 4 cm was found which is not different from idings in the normal population Increasing caecal ter during the puerperium gives rise to suspicion of ecum In 90% of the patients free subdiaphragmatic sappeared by the 5th day after Caesarean section

ration of the caecum with overdistension d by obstruction of the distal colon has been ibed many times in the literature (1 10 14 16) taneous perforation of the caecum in connec with paralytic ileus where no mechanical ob tion could be found during surgery is ex ely rare (7 12 22)

ost frequently perforation occurs on the anterior ne of the caecum 5 cm distal to the ileo-caecal m Based on clinical and experimental studies ral theories have been advanced as to the reason dilection for this site and there are several butory factors (5 10 16 19 20 21)

cl ni al symptoms of perforation and immi perforation of the caecum are often non eristic and few (1 5 14 16) In order to s a radiological measurement of the largest ter of the caecum in cases of obstruction of the n Lowman & Davis Davis & Lowman (1957) ed 12 cases with imminent perforation and 7 caecal perforation In these 19 patients they found caeca varying in diameter between 9 0 and 16 3 cm In a series comprising 100 subjects without previous intestinal disease colon examinations with barium and air insufflation were made The average greatest caecal diameter was 6 5 cm and in 97 the diameter was less than 9 cm Lowman & Davis concluded that a caecal diameter of 9 cm or more indicated imminent intestinal perforation and in these patients surgical intervention would always be necessary In cases described in the literature the surgical treatment in imminent perforation and caecal perforation was mainly caecostomy (1 10 12 16) The mortality in connection with caecal perfora tion is high varying between 44% and 72% (1 10) Lowman & Davis found a mortality of only 8% if surgery was carried out before perforation occurred (12 cases)

Several reports are available on colonic obstruc tion with distension of the caecum and caecal perfo- ration following normal delivery and Caesarean sec tion (2 3 8 13 17) Only 5 cases of caecal perfora tion associated with paralytic ileus following Caesarean section have been reported (6 9 11 15) In these 5 patients the symptoms were few and non-characteristic as in other acute abdominal dis orders occurring during the puerperium Common features in all were raised temperature raised pulse rate varying abdominal distension and pains mainly in the right iliac fossa In none were there clinical signs of mechanical obstruction Only one patient presented with signs of irritation Only in the case described by Kålund Jensen was a caecal diameter of 10 cm revealed on repeated examination of the radiographs Based on the case reports it is difficult

Table I *Indications for Caesarean section in 100 patients*

Cephalopelvic disproportion	21
Incoordinate labour	13
Malpresentation	11
Prolapse of cord	10
Asphyxia	9
Previous caesarean section	7
Placenta previa	6
Abruptio placentae	6
Elderly primigravida	6
Toxaemia	3
Other causes	8
Total	100

to ascertain the interval between the caecal perforation and surgery but in 3 patients (9 11) free gas under the diaphragm was present on the 5th day after Caesarean section and surgery was not performed until the 6th or 7th day In these the free gas was taken to be caused by the preceding Caesarean section However it has previously been proved that air introduced into the abdomen at laparotomy is usually absorbed within 5 to 7 days (11 18)

These 5 cases of caecal perforation and paralytic ileus after Caesarean section in which the symptomatology was limited and the surgical findings surprising stimulated the present investigation to determine the greatest caecal diameter following normal Caesarean section and to determine how quickly residual air in the abdomen disappears after Caesarean section

MATERIAL AND METHODS

The study comprised 10? patients who had undergone Caesarean section over a one year period in the maternity ward at St Joseph s Hospital The indications for Caesarean section are shown in Table I Fifty of the 10? patients were primigravidae Their ages varied from 17 to 41 years with an average age of ?7 years The group studied comprises all patients with a normal course of

Table II *Caecal diameter measured on the 3rd and 5th day after Caesarean section*

Day	Number	Mean (cm)	Range (cm)	S D
3	99	6 7	5–9 5	0 99
5	97	6 0	4 5–8 5	0 08

S D Standard deviation

Table III *The amount of free gas in the abdomen measured on the 3rd and 5th day after Caesarean section*

Day	Number	Mean (cm)	Range (cm)	S D
3	100	0 16	0–1 0	[illegible]
5	100	0 0?	0–0 4	[illegible]

Caesarean section and puerperium Two patients were excluded one of them underwent appendectomy on the [illegible] day after Caesarean section and for the other [illegible] graphs were not satisfactory ?6 were elective sections and 74 patients were in labour

As anestesia for Casearean section a combination of succinylcholine thiapental sodium with nitrous oxide and oxygen was used

On the 3rd and 5th day after Caesarean section [illegible] radiographs of the abdomen were taken in the [illegible] position Each radiograph showed the diaphragm [illegible] and the caecal region The assessment of the greatest caecal diameter without using contrast *sent any difficulties* In 3 patients it was not possible on the radiograph to locate the caecum because of too little gas and no fluid level

The amount of free gas in the abdomen was measured [illegible] the greatest border of gas under the diaphragm

RESULTS

Table II shows the average greatest diameter of the caecum on the 3rd and 5th days after Caesarean section There is no statistically significant difference in the caecal diameter measured on the 3rd and the 5th days at 95% level (Student s t test)

On the 3rd day 4 patients had a caecal diameter ranging between 9 and 9 5 cm None of these presented any clinical signs of mechanical obstruction but one was treated with suction and parenteral fluids because of vomiting Three of the 100 patients vomited during the puerperium and were therefore treated for short periods with suction and parenteral fluids On the 5th day all patients were completely well

On the 3rd day following Caesarean section the survey radiographs in 26 patients showed small fluid levels but only 4 of these presented a similar picture on the 5th day In none of the patients had the caecal diameter increased by the 5th day but [illegible] there was no decrease

In the group of patients where elective Caesarean section was used nobody had signs on paralytic [illegible]

e puerperium and all had a caecal diameter r than 9 cm

54 patients no free gas in the abdomen could be d radiologically on the 3rd day after Caesarean on and on the 5th day 90 patients had no free In all patients the amount of subdiaphragmatic was less on the 5th day as compared with the 3rd

DISCUSSION

ie present study an average caecal diameter of m was found No significant difference in aver caecal diameter was found between the 3rd and day after Caesarean section In their control p Lowman & Davis found an average caecal eter of 6 5 cm

n the 3rd day after Caesarean section only 4 ents had a caecal diameter of 9 cm or more and e of them presented specific or particularly pro nced clinical symptoms One was treated with ion and parenteral fluids All the patients had ced caecal diameters on the 5th day after sarean section Lowman & Davis stated that a neter of 9 cm or more indicated imminent perfo on of the caecum and concluded that surgical rvention would be necessary in such cases

lone of the 4 patients with a caecal diameter of 9 or more was treated with enema Kålund Jensen advised against enema in cases of paralytic ileus caecal distension because a pressure of 100 cm) is commonly used to introduce an enema and pressure might be transmitted to the caecum cause perforation Millar & Øvlisen (11) found assumption to be of importance because on vious occasions caecal perforation had been ob ved both clinically and experimentally at intra of from 20 to 50 cm H_2O (19 21)

y showed that the amount of free gas left the abdomen after Caesarean section is very In only 50% was it possible to find a slight of free gas in the abdomen on the 3rd day Caesarean section In 90% no gas was evident 5th day

CONCLUSION

rvey radiography of the abdomen without using ast media in the colon is well suited for as aecal diameter after Caesarean section

During the puerperium after Caesarean section the average caecal diameter was 6 4 cm This does not differ from previous findings in the general popula tion

In patients with distension of the abdomen and increasing caecal diameter during the puerperium after Caesarean section the danger of caecal perfo ration should always be borne in mind At the same time it must be remembered that the amount of free gas in the abdomen following Caesarean section is always very small and will have disappeared in 90% of patients by the 5th day after operation

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THE USE OF ISOXSUPRINE IN ESSENTIAL DYSMENORRHEA

A controlled clinical study

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stract The uterus specific beta adrenoceptor stim lator isoxsuprine was used for the treatment of prim y dysmenorrhea in a double blind controlled clinical dy No significant beneficial effect of the drug was ident

ta adrenoceptor stimulating agents are frequently ministered in an attempt to inhibit premature bour Theoretically it might be expected that se agents could be of some use in the treatment dysmenorrhea Dysmenorrhea is listed as an indi tion for the use of isoxsuprine (Cardilan Ferro- n) in the Norwegian drug index (Felleskatalogen) wever apart from one uncontrolled study (2) no nical study has been undertaken to see whether xsuprine really is effective in the treatment of smenorrhea A controlled double blind clinical al of isoxsuprine against placebo in the manage nt of dysmenorrhea is reported here

MATERIALS AND METHODS

male Medical and pharmacy students were asked at a ture to volunteer for the project 30 students were en led 29 were nulliparous 1 primiparous One had an D the others used other types of mechanical con ception 18 had severe dysmenorrhea 12 of these had stay in bed for one day each period The other 12 had derate dysmenorrhea which means that they could ction (attend le tures etc) with the use of analgesics e participants were instructed to take tablets for two ys before the beginning of menstruation and for as many ys as they usually had pain The tablets were isox rine 20 mg×3 or placebo tablets identical in appear ce Two consecutive menstrual cycles were used one th isoxsuprine and one with placebo for each partici nt. The type of tablets taken during the first cycle was ndomized The participants were told that some of them ght get placebo tablets but they did not know that each them would get one cycle with the active drug and one le with placebo

The participants were questioned about the following The effects of the drug 2) Side effects (the options palpitations dizziness headache tendency to faint nausea were especially mentioned to them) 3) When men struation started related to when they started taking the tablets 4) Whether the menstrual loss was heavier or lighter than usual 5) Whether they wanted to go on using the tablets

RESULTS

Twenty six of the participants completed the trial One of those who did not complete did so because of side effects of the first course of tablets (which was placebo) for the other three the reasons were not related to the tablets

Of the 26 who completed 14 did not have any relief of dysmenorrhea either with isoxsuprine or with placebo One person had relief of pain both with isoxsuprine and with placebo Seven had relief of pain with isoxsuprine and not with placebo while 4 had relief of pain with placebo and not with isox suprine This difference is not statistically signifi cant Of the persons reporting relief of pain only one reported complete relief while the others re ported some relief

Six persons reported side effects 5 with isox suprine and one with placebo The side effects of isoxsuprine were dizziness (2) quivering and dizzi ness (1) nausea (1) and headache (1)

Whether isoxsuprine had been taken for two or more days before the onset of menstruation or had been started on the same day as the bleeding was not related to its effect

There was no tendency for isoxsuprine to prolong the menstrual cycles No significant change in the amount of menstrual loss was noted

Three of the 8 persons who apparently benefited from isoxsuprine indicated that they wanted to go on taking the tablets and all of the 5 persons who had benefited from placebo wanted to go on taking those

DISCUSSION

This investigation shows that isoxsuprine has no significant effect in the relief of essential dysmenorrhea While this study was in progress the same results were reported for hydroxyphenyl orciprenalin (Berotec) another beta adrenoceptor stimulating agent (1) It must be concluded that beta adrenoceptor stimulation is ineffective in relieving menstrual pain

ACKNOWLEDGEMENT

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CERVICAL BACTERIAL FLORA IN WOMEN FITTED WITH A COPPER RELEASING INTRA UTERINE CONTRACEPTIVE DEVICE (IUD)

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stract A bacterial culture was taken from the cervix in sexually active women before and 3 and 6 months er insertion of either a copper releasing or an inert ra-uterine contraceptive device (IUD) Sixty had a pper T (TCu 200) and 25 a Lippes loop D Although more than a quarter of the patients the bacterial flora eased slightly in diversity and abundance after IUD ertion there was no difference in effect between the u-200 and Lippes loop D

tra-uterine infection septic abortion and septic mia have been attributed to the use of intra rine devices (IUDs) Despite the wide spread e of this method of contraception there have been w reports of serious pelvic infections with a con ntional inert IUD *in situ* (6) Recently however e Dalkon Shield has been reported to cause se us and even fatal infections during the second mester of accidental pregnancy (1 6 9) The ultifilament string unique to the Dalkon Shield , by capillary action provide a mechanism pathogenic bacteria from the vagina enter rine cavity (13) Mishell et al (7) showed by transfundal sampling that there were bacteria the uterine cavity after insertion of an IUD (Lip loop) However the incidence of positive cul diminished rapidly and all endometrial cavi studied were free of bacteria within one month insertion Other studies have also shown that the esence of inert IUDs does not increase signifi the incidence of positive cultures in the dometrial cavity (17 18) Fiscina et al (3) demonstrated the gonococcicidal tion of copper *in vitro* but this observation has not been confirmed *in vivo* In fact Spellacy et al (11) found that copper releasing IUDs do not prevent gonococcal infection The aim of this study was to investigate whether copper releasing IUDs have an adverse effect on the cervical bacterial flora under *in vivo* conditions

MATERIALS AND METHODS

Eighty five healthy parous and sexually active women who had requested IUD insertion were chosen for study The Copper T (TCu 200) group consisted of 60 women and the Lippes loop (type D) group which served as a control of 25 women The age structures of the two groups are shown in Table I

All IUDs were inserted postmenstrually Before inser tion a cervical swab was taken for bacterial culture and a Papanicolaou smear and vaginal swab for yeast and *Tri chomonas vaginalis* screening The same examinations were repeated 3 and 6 months after IUD insertion

The cervical swab was sent to the laboratory in a trans port medium (modified Stuart medium ref 8) The swab was cultured on normal blood agar plates in 5% defibri nated sheep s blood on a lactose agar plate on a choco-

Table I *Age distribution in TCu 200 and Lippes loop D groups*

Age	TCu 200 (%)	Lippes loop D (%)
20–25	2 6	6 6
26–30	27 6	23 3
31–35	42 1	26 6
36–40	23 6	10 0
41–45	3 9	26 6
46–	1 3	3 3

Table II *Bacteria possibly present in normal vaginal flora*

Döderlein bacillus groups
Apathogenic spirochaetes
Diphtheroids
Staphylococcus albus
Non haemolytic streptococcus
Streptococcus viridans
Escherichia coli
Streptococcus faecalis
Staphylococcus aureus sometimes
Mycoplasma hominis types I and II

late agar plate and on a medium for gonococcus (gc medium) (10 14) After these cultures had been set up the stick was used to inoculate a liver broth tube The plates were incubated at 36 C the chocolate agar and gc medium plates in the presence of CO_2 (from 5% to 10%) and examined after 24 and 48 hours The extent of bacterial growth was estimated and recorded on scale from + to +++ The bacteria were identified by standard methods (4) and the drug sensitivities of the different types were determined by Ericsson s disc technique (?) A culture was considered negative when even in the liver broth medium no growth was observed after 72 hours incubation

The bacteria seen in vaginal cultures from apparently healthy women are listed in Table II

RESULTS

All the patients were free from *Neisseria gonorrhoeae* before insertion of the IUD and no gonorrhoeal infection was found in either group at check ups after 3 or 6 months During the study one positive *Trichomonas vaginalis* culture was found in each group at the 3 month check up The patients with trichomonal infection were treated with metronidazole (Trikozol® Medipolar Oy Oulu Finland) 200 mg three times daily for 7 days by mouth (the male partner was treated likewise) and locally with povidone iodine (Betadine® Leiras Oy Turku Finland) for 10 days Yeast infection was more common in the Copper T group both before

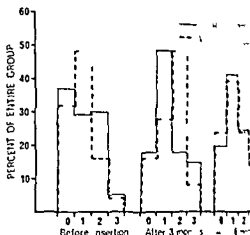


Fig 1 Proportions of women harbouring none to th... more bacteria in the cervix before insertion of the I... and 3 and 6 months later

insertion (6 cases) and during the course of ... study (Table III) *Candida* infection was tre... locally either with nystatin vaginal tablets 1... I U (Nystacid® Läike Oy Turku Finla... with natamycin vaginal tablets 25 mg (Pimafu... Mycofarm Delft Holland) at night for ? weeks the routine Papanicolaou smears there we... signs of malignancy

The events associated with the use of th... IUDs are recorded in Table IV There were ... accidental pregnancies in the Lippes loop g... (one ectopic for which salpingectomy was p... formed and one spontaneous abortion w... Lippes loop D *in situ*) but none in the Copper group No patients showed any signs of pelvic ... flammatory disease (PID)

The results obtained from the cervical cultu... grouped according to the number of differe... of bacteria before insertion and 3 and 6 mo... afterwards are shown in Fig 1 The number of b... teria increased slightly in both groups

As judged from the growth in the cultures 16 ... tients (26 6%) in the Copper T group and 7 ...

Table III *Trichomonas vaginalis and Candida albicans cultures from vaginal swabs before and 3 and 6 months after insertion of TCu 200 and Lippes loop D*

	Number of patients	Trichomonas vaginalis			Candida albicans		
		0	3	6	0	3	6
Lippes loop D	25	–	1	–	–	5	1
TCu 200	60	–	1	–	6	14	10

abl IV Termination associated with six months e of TCu 200 and Lippes loop D by the respective oups

	TCu 200	Lippes loop D
mber of patients	(60)	(25)
egnancy	–	2
pulsion	2	–
in and or bleeding	1	2
rsonal reasons	1	–
tals	4	4

the Lippes loop group had a more abundant bac ral flora after 6 months of an IUD use than be re insertion The resistance of the bacteria to biotics and chemotherapeutic agents did not ter during the course of the study

DISCUSSION

s earlier suggested that copper and its salts have de bactericidal activity (12) Of the micro-ganisms tested *in vitro* the only one that was ns tive to cupric salts was *Neisseria gonorrhoeae*). As we found no differences between the Cop-r T and Lippes loop groups 3 and 6 months after sertion our study confirms that copper *in vivo* s no adverse effect on the cervical flora

Although the cervical bacteria are slightly more undant after insertion of an IUD no cases of PID ere found in this study By direct transfundal mpling Mishell et al (7) showed that the endo-etrial cavity is highly resistant to single non petitive bacterial contamination some 80% of e uteri they studied were already bacteria nega te within 48 hours of IUD insertion In our two ge scale studies (15 16) for the evaluation of Copper T 200 and Copper T 300 where a total of 09 Copper T insertions were made and more an 44000 women months of use monitored the fection rate during the first year of use estimated y the life table method was only 1% In the hole series only one severe case of PID was en countered

Our study confirming the results of previous ytological evaluation (5) demonstrated that al hough vaginal bacteria were slightly more abundant IUD users than among other women there was o difference between the inert and copper releas ng IUD groups

The study also shows that during IUD use the resistance of these bacteria to antibiotics and chemotherapeutic agents does not alter

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INDUCTION OF THE PREGNANCY ZONE PROTEIN BY CONJUGATED OESTROGENS

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tract Treatment with conjugated oestrogens was ignificantly the serum concentration of pregnancy zone protein (PZ) in a group of post women The basic level of PZ before treat was comparatively high in this group of women and t be related to age and previous pregnancies Natur y occurring conjugated oestrogens have a similar effect the induction of PZ as synthetic oestrogens

he induction of the pregnancy zone protein (PZ) is lieved to be oestrogen-dependent (5 6 17) Con ntrations about 100 mg/100 ml of this high mo cular weight serum α_2-glycoprotein (4 13 14 , 18) are found during late pregnancy and after livery there is a rapid decrease to nonpregnant vels (<4 mg/100 ml) (15)

Exogenous administration of synthetic oestro- ns is also known to increase the serum concentra on of PZ in nonpregnant women and men (1 2 6) The induction of PZ seems to be affected by the pe and dosage of treatment (2 6) In a previous udy of women treated with combined oral contra ptives 1 mg norethisterone + 0 1 mg mestranol nett®) was found to be a more potent in ker than 0 5 mg norgestrel + 0 05 mg ethinyl tradiol (Follinyl®) while 0 3 mg norethisterone ini-P®) gave no measurable increase of PZ (6) hen given to men with prostatic cancer a combi on of polyoestradiol phosphate (Estradurin®) d diethylstilboestrol (Stilbol®) or diethylstil oestrol only was found to induce PZ while poly tradiol phosphate only gave no measurable in rease (?)

Previou ly the effect on the synthesis of PZ of ogenously administered oestrogen has been in gated using synthetic oestrogens Conjugated rally occurring oestrogens are used in treatment of oestrogen deficiency in post menopausal women and the side effects on blood coagulation (9) liver function (3) and lipid metabolism (12) are believed to be less pronounced than with synthetic oestrogens Little is known about the influence on the synthesis of PZ

The recent development of a highly sensitive radio-immunoassay for PZ (7) has made it possible to study the low levels of this protein in untreated nonpregnant women Most previous studies on this protein have been made on young women taking oral contraceptives or on women during pregnancy In the present investigation the concentration of PZ was measured by radio-immunoassay in post menopausal women before and during treatment with conjugated oestrogens

MATERIAL AND METHODS

Venous blood samples were drawn from women at ending the Department of Obstetrics and Gynaecology University of Umeå for post menopausal symptoms profuse sweatings and hot flushes being the commonest 34 women were investigated before treatment All women were apparently healthy taking no other drugs 31 of these women were investigated also after two months of treatment with 1 25 mg Promarit® six days per week Promarit® contains naturally occurring conjugated oestrogens mainly oestrone sulphate and equilin sulphate prepared from pregnant mare urine

After coagulation all sera were decanted and stored at −70°C until use Samples were coded and tested blindly in duplicate The concentration of PZ was determined by a radio-immunoassay (7) based on determination of ^{125}I labelled PZ using monospecific rabbit antiserum and the purified protein as a standard (13 14) Separation of free and antibody bound PZ was performed with the double antibody solid phase method (DASP) (10) and the range for measurements was 50-2000 ng PZ/ml (7)

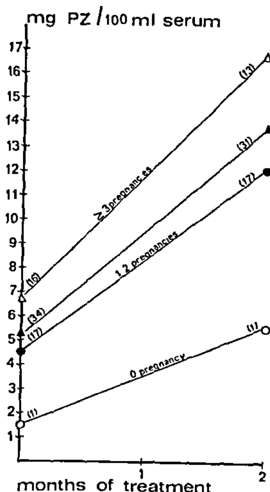


Fig 1 Mean concentration of the pregnancy zone protein in sera of women before and after two months treatment with conjugated oestrogens (Promarit®) The total material (▲—▲) is divided according to previous pregnancies Number of women is indicated within parentheses

RESULTS

Some characteristics of the investigated women are presented in Table I

All women were found to have measurable basic levels of PZ and an increase in PZ concentration was found in all individual women after two months of treatment The mean serum concentration of PZ in 34 women before treatment was 5 3±0 6 mg/100 ml (mean±S E M) After treatment with conjugated oestrogens (Promarit®) for two months the mean serum concentration for 31 women was 13 9±1 7 mg/100 ml (mean±S E M) (Fig 1) The increase was significant ($P<0\ 01$)

The women were grouped according to previous pregnancies as shown in Fig 1 The mean value of the concentration of PZ before treatment for 16 women with 1–2 previous pregnancies was 4 [illegible] mg/100 ml The corresponding figure for women with 3 or more pregnancies was 6 7±1 1 mg/100 [illegible] For both these two subgroups the increase of [illegible] after two months of treatment was statistically significant ($P<0\ 01$) and reached levels of 12 [illegible] and 16 9±3 3 mg/100 ml respectively The [illegible] woman with no previous pregnancy increased [illegible] PZ concentration from 1 5 to 5 6 mg/100 ml

DISCUSSION

During treatment with conjugated oestrogens (Promarit® 1 25 mg daily 6 days per week) all the women increased their concentration of PZ from two up to five times This study thus gives further evidence for an oestrogen dependent PZ-synthesis

All women had measurable amounts of PZ before treatment and the basic levels were high when compared to levels earlier observed in young women (15–25 years of age) with basic PZ concentrations below 1 mg/100 ml (8)

As shown in Fig 1 the number of previous pregnancies might be of importance for the basic level of PZ and may furthermore affect the concentration of PZ after hormonal treatment The material is however too small to allow definite conclusions Present studies of the effect of age and previous pregnancies on the PZ concentration seem to confirm these results (8)

This study indicates no straight dose-response relation between the oestrogen level and the basic PZ concentration The group of elderly women with symptoms of oestrogen deficiency shows higher amounts of PZ than younger women The observed increase in PZ concentration is lower than during pregnancy when the mean level in the last trimester is around 100 mg/100 ml (15) The duration of treatment was however only two months During treatment with combined oral contraceptives levels between 15 and 50 mg/100 ml can be seen (6) [illegible]

Table I

Number of patients before treatment	34
Number of patients after two months of treatment	31
Mean age in year ±S D	[illegible] 1+4 9
Interval since last menstruation	4 months 8 years

treated with conjugated oestrogens for post symptoms induce PZ in concentrations ch are equal to those observed for young women with combined oral contraceptives Pro-[8] which only contains naturally occurring oestrogens acts in this respect similar synthetic oestrogens

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IN VIVO DETERMINATION OF THE STRESS-STRAIN RELATION OF THE HUMAN MYOMETRIUM

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ract Smooth muscle is capable of responding by con-tion to mechanical distension Neither the structural s for this phenomenon nor the theories of smooth cle behavior are *completely clear A method is now* ribed by which the contractile response to mechani distension of the human uterine muscle in vivo is mined The distension is enforced sinusoidally with-e frequency range 0 005–2 Hz by filling and emptying ber balloon introduced into the uterine ca ity A metric index of the myometrium is defined using s law after the approximate evaluation of a contrac modulus and the tangential stress and strain in the in layer of the uterine wall The regression line of in s upon frequency is calculated and intercept and re sion coefficient of the equation *for basic conditions* compared with those obtained during administration of macologically active agents It is suggested that the erences in intercepts and regression coefficients be d as a measure of drug effect

effect upon the uterine muscular wall of phar cologically active agents has most often been ex ssed in terms of modification of intracavitary ing pressure amplitude and frequency of con tion Intrauterine pressure is however a com n function of the tension within the muscular l its curvatur and thickness In addition spon eous changes in myometrial activity complicate le luation of drug effects on the basis of pres e measurements calling for greater insight into mod fication of muscular responses to well fined specific stimuli

Strips of smooth muscle tested in vitro as well s oo h muscle in vivo are capable of responding to ra tion to mechanical distension Neither structural basis for this phenomenon nor the ories of smoo h muscle behavior are completely clear Experiments on intestinal smooth muscle do support the contention that the sliding filament he ory which quantifies a length active tension rela tionship can be extended to smooth muscle (7) But there is a wide variety of muscular behavior which does not conform to any of the well known hypotheses of muscular function Examples are phenomena such as stress relaxation equivalent to adaptation following step-wise strain and stress re sponse to sinusoidal strain A model is therefore needed which accounts for mechanical properties on the basis of physical as well as chemical changes Pending this a technique has been designed which might serve as a tool for the classification of para meters to be looked for in the determination of drug effects on the uterine muscle

TECHNIQUE

The aim has been to record and analyze the devel opment of tension in the uterine myometrium as a contractile response to distension The filling and emptying of a thin walled rubber balloon placed in the cavity of the organ was chosen to induce the mechanical stimulation The balloon serves as a re ceptacle for predetermined quantities of fluid pumped into and withdrawn from it in sinusoidal sequences Proportional distension of the wall of different sized uteri is achieved by using balloons and matching pump systems of varying dimensions Each of these units has been ma hined to cater for the influences of dynamic processes on the meas urement of pressure

A bellows pump is connected to a transmission tube ending in a stem with several perforations (Fig

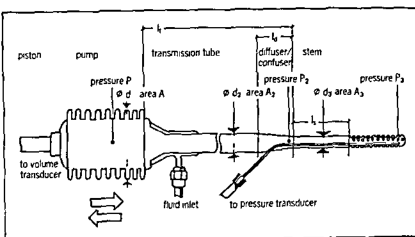


Fig 1 Mechanical device fo oidal distension of the uter The thin walled rubber ballo mounted without leakage aro perforated part of the s em

1) Around the stem to be placed inside the uterus a thin walled rubber balloon is attached and checked for the absence of leaks Inside the intra uterine stem and partly within the transmission tube a cannula with a small diameter is placed This cannula tube is used for pressure transmission and ends in one of the perforations to avoid dis turbances from the streaming fluid All the other openings in the stem serve as connections between the interior of the stem and the interior of the balloon

The bottom of the bellows is connected to a piston governed by an eccentric mounted on the end axis of a shunt wired electric motor of DC type with constant voltage over the field but not over the armature Variable speed transmission within the range 0 005–10 rotations per second is achieved with a thyristorized current control and a two-step echanical gear The feed back of a tachometer nerator ensures a constant speed at each setting Mechanical connection between the bottom of the bellows and a linear precision potentiometer effects the monitoring of volume in the balloon as a func tion of time on one channel of a dual beam storage oscilloscope The instantaneous pressure in the bal loon which does not take any tension is con sidered equivalent to the overall pressure in the uterine cavity and recorded on the other channel of the oscilloscope by means of a pressure transducer

HYDRODYNAMIC CONSIDERATIONS

The following requirements have guided the dimen sioning of each unit

1 The entire system shall be inelastic and must not contain gas or vapor at any time

2 The intracavitary pressure shall be dete correctly

To achieve this the instantaneous cha volume in the balloon must for example b chronous with the change of volume in the b pump Furthermore pressure losses which from either friction or inertia during move fluid in the system shall be minimized

EQUATION SYSTEMS

V_0 is defined as the bellows displacement fr middle position to one extreme The volu intrauterine balloon (V) is a function of tim cording to

$$V = V_0 \sin \omega t$$

ω being the angular frequency in radians/s *volume flow* (Q) is determined by the equat

$$Q = \frac{dV}{dt} = V_0 \omega \cos \omega t$$

and *volume flow acceleration* ($\dot{Q}$)

$$\dot{Q} = \frac{d^2V}{dt^2} = -V_0 \omega^2 \sin \omega t$$

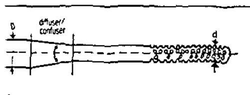
The *flow velocity* (v) in any part of the area A_i is

$$v = \frac{1}{A_i} V_0 \omega \cos \omega t$$

and *flow acceleration* (a)

$$a = -\frac{1}{A_i} V_0 \omega^2 \sin \omega t$$

Prerequisites for the validity of equa se (5) are that the system is rigid the fluid in



2 The construction of the diffuser/confuser which ...ecessary to avoid the risk of cavitation

...le and that cavitation phenomena do not occur ...owing the transmission tube to assume almost ... same diameter as the bellows and avoiding ...rp angles between the transmission tube and the ...m by using a diffuser/confuser minimizes the ...k of cavitation

...mpirically such a diffuser (Fig 2) shall have a ...angle (α) of less than 7–8 if the Reynold number ...d/ν) is high e g 5000–10000 ... being the flow ...ocity d the diameter of the canal and ν the kine...tic viscosity The length of the diffuser (l_d) is re...ted to the diameters of the neighboring channels ...the equation

$$\frac{D-d}{2\tan(\alpha/2)}$$

...quations (1) to (5) can be utilized to define the ...ssure losses in the system at the crucial mo...ents when the influence of inertia or friction is ...imal

The pressure loss due to inertia (ΔP_i) is of great importance at the moment of reversal of flow ...en the volume flow acceleration is minimal and ...ωt=1 (Fig 3)

On the basis of Newton s first law $F=m\,a$ (force ...als acceleration times mass) and considering ...

$$\Delta P_i \; A$$

$$\varrho \; l \; A_i$$

$$\frac{V_0}{A}\omega^2$$

...ere ϱ is the density of the fluid and l_i the geo...ric length of the tube

...minimal pressure difference $\Delta P_i = P_1 - P_3$ due ...inertia is

$$-16\pi f^2 \; V_0 \varrho \left(\frac{l}{d_2^2}+\frac{l}{d_3^2}\right)$$

...being the frequency in cycles per second (Hz) ...ed to the angular frequency by $f=\omega/2\pi$ and l ... the lengths of the transmission tube and the stem respectively The location of the diameters d_2 and d_3 is shown in Fig 1

The *pressure loss due to friction* (ΔP_f) is maximal when flow velocity reaches its lowest value e g 90° after the loss due to inertia is maximal (Fig 3) It is assumed that during the withdrawal phase of the cycle the total pressure in the *intrauterine stem* is equal to atmospheric pressure This means that the pressure loss in the inlet holes in the intrauterine stem is negligible and that the pressure in the bal*loon is at least atmospheric The most critical point* is located at the border between the stem and the diffuser P_2 (Fig 1) The diffuser gives a pressure recovery of about 70% of the dynamic pressure which increases the static pressure in the transmission tube

The Bernoulli s equation gives

$$P_3 = P + \frac{\varrho v^2}{2} + h$$

$$h = \lambda \frac{l \varrho v^2}{2d}$$

$$\Delta P_f = \frac{32 \varrho V_0^2 f^2}{d_3^4}\left(1+\lambda\frac{l}{d_3}\right)$$

$$\Delta P_f = P_3 - P_2$$

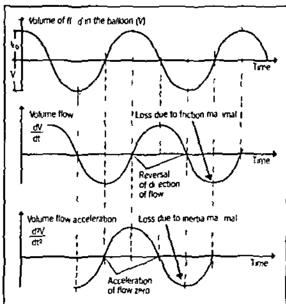


Fig 3 Time relationship between the filling of the balloon the volume flow and the volume flow acceleration The critical points when pressure losses due to friction and to inertia are maximal are indicated

Table I *Units for mechanical excitation of the myometrium*

	Unit no 1	Unit no 2	Unit no 3	Unit no 4
Oscillation volume ml	0 1–0 6	0 4–2 1	2–1[illegible]	4–3[illegible]
Length of transmission tube l_t mm	300	300	300	<[illegible]
Diameter of transmission tube d_t mm	6	10	20	[illegible]
Length of stem l mm	80	100	100	100
Diameter of stem d_s mm	2 5	3 5	6	8 5
Length of diffusor l_d mm	8	20	70	170

where v is velocity of the fluid h the pressure loss in the stem and λ a friction factor which has the numerical value of about 0 02 for the tubes used in this system

The pressure losses in the holes of the intrauterine stem must be minimized which is done by having as many holes as possible The pressure difference ΔP_h over the holes between the inside of the stem and the intrauterine balloon is determined by the equation

$$\Delta P_h = \xi \frac{\varrho v_h^2}{2}$$

where v_h is the fluid velocity in the holes The coefficient of pressure loss ξ is 0 4 if the holes are poorly machined e g have sharp edges The value decreases to about 0 01 if the edges are rounded with a very small radius The pressure loss in the perforations will be negligible if the total area of the holes is made to exceed the area of the intrauterine stem by a factor of 3–4 and if the machining is good

It is evident that the frequency of the sinusoidal fluid movement is limited by the volume required to [illegible]ide sufficient distension of the uterine wall and the relation between lengths and diameters of the transmission tube and the intrauterine stem The smallest diameter of each unit is that of the stem which with the empty balloon around it has to be introduced through the cervical canal preferably without dilatation A stem 7 mm in diameter can be used during pregnancy until the 14th week but about 4 mm outer diameter is the upper limit for non pregnant uteri The dimensions of the various components of four different units are given in Table I

PERFORMANCE CHARACTERISTICS

The performance characteristics of the units were checked in an experimental set up using a large diameter water filled plastic basin as a uterine dummy The increase in static pressure as a [illegible] of the transport of fluid between pump and [illegible] was insignificant Volumes of fluid close to the maximal capacity of each unit were oscillated and the resultant change in dynamic pressure was recorded The results are given in Table II If one accepts the generation of a dynamic pressure [illegible] ≤5 mmHg unit number 4 should not be used [illegible] frequencies above 6 Hz It made no difference [illegible] the results whether the rubber balloon enclosed the stem or not This shows that properties of the [illegible] of the balloon do not influence the recording [illegible] muscle response

EVALUATION OF THE RECORDINGS

The measurements are made at distinct frequencies of mechanical excitation The recordings are evaluated on the basis of the volume of fluid used for the distension (V_{osc}) the frequency of distension [illegible] and changes in intrauterine pressure (ΔP_i) The [illegible] rine dimensions are determined from bimanual palpation in the frontal and sagittal planes and [illegible] sound measurement The thickness of the uterine wall (h) is defined empirically as 1 0–1 25 cm (Table III) The uterine cavity during early pregnancy [illegible] considered to represent a hollow ellipsoid with the volume $V_i = \frac{4}{3}\pi r_f r_s b$ In this equation [illegible] the sound measurement of the corpus [illegible] ment while $2(r_f+h)$ is the palpation measurement in the frontal and $2(r_s+h)$ the palpation measurement in the sagittal projection

To obtain a quantity which will serve to characterize the functional state of the myometrium [illegible] well as the effect upon it of pharmacologically [illegible] tive agents a tonometric index of the myometrium [illegible] is defined For this one has to accept several [illegible] proximations The mechanical distension of the [illegible] uterine muscle for example is taken to be [illegible] that the intraabdominal extrauterine pressure [illegible]

ble II Development of dynamic pressure mmHg in the high frequency range

	Frequency of oscillation Hz						
	10	9	8	7	6	4	2
#1 Osc vol 0 6 ml	3 5	3 0	2 0	<2	<2	<2	<2
#3 Osc vol 10 ml	6 0	5 0	4 0	3 0	2 0	<2	<2
#4 Osc vol 28 ml			8 0	6 0	4 5	2 0	0

nged during the measurement procedure The rine wall is furthermore considered to be in mpressible i e the volume of the uterine wall is before and at maximum distension

n the mathematical model used to characterize tonometric index the conditions in an imagined tion through a rotation ellipsoid at the *sym rical rotation radius* (r) are studied

$$\left(\frac{3}{4\pi}\frac{V_t+V_0}{b}\right)^{\frac{1}{2}}$$

irstly the *contractile modulus* (m) i e the ratio ween the relative strain and the relative contrac n of diameter is defined The equation can have following approximate expression provided the gnitude of the distension is small

$$\frac{1-\frac{r}{R}}{\frac{r}{R}\left(1-\frac{b}{B}\frac{r}{R}\right)}$$

being ($r+h$) and B ($b+h$)

As the second step the *tangential stress* (σ_t) in innermost layer of the uterine wall is estimated order to obtain equivalent expressions for preg nt and non-pregnant uteri the imagined section the rotation ellipsoid is treated as part of a cylin

$$= [P_i(R^2+r^2)+P_u 2R^2]\frac{1}{R^2-r^2}$$

The subscripts in the equation denote t tangen al, i inner and u outer

Table III *Thickness of the uterine wall*

Pregnancy after last menstrual period	cm
3rd week	1 0
15th week	1 25
16th week	1 0

In order to eliminate the outer pressure the stress-difference $\Delta\sigma_t=\sigma_{t_i}-\sigma_{t_0}$ is derived

$$\Delta\sigma_t\approx\Delta P\frac{1+(r/R)}{1-(r/R)}$$

As the distension is small the differences be tween R_1 and R_0 r_1 and r_0 B_1 and B_0 and b_1 and b_0 are minute

$$\frac{r_1+r_0}{R_1+R_0}\frac{b}{B}\approx\frac{rb}{RB}$$

Calculating the *stress-difference in an axial direc tion* (σ_x) in the inner layer of the same section through the ellipsoid gives the analogous expres sion

$$\Delta\sigma_x\approx\Delta P\frac{(r/R)^2}{1-(r/R)^2}$$

Obviously $\Delta\sigma$ (*stress difference in the radial direction*) equals $-\Delta P$

The third step is to form an expression for the *tangential strain* ε_t Differentiating the equation for the uterine volume

$$V=\frac{3}{4}\pi\ r^2b$$

gives the relation

$$\frac{dV}{V}=2\frac{dr}{r}+\frac{db}{b}$$

Two cases can be viewed namely

1) $db/b=0$ and the difference in tangential strain $\Delta\varepsilon_t=0.5\ (dV/V)=0.5\ (V_{osc}/V)$ when there is an ex treme eccentricity of the rotation ellipsoid i e it approximates a cylinder and

2) $db/b=dr/r$ and $\Delta\varepsilon_t=\frac{1}{3}\ (V_{osc}/V)$ when the ec centricity equals 1 i e the structure is sphere like The first relation is used for the non pregnant and the second for the pregnant condition

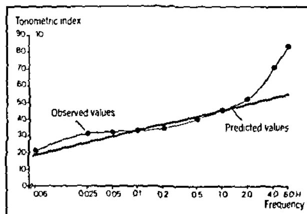


Fig 4 The row of frequency bound tonometric indices observed *in one indomethacin treated pregnant* woman together with the line of regression of *the index values* on *log* frequency the equation $y=45\ 1+12\ 3x$ is based *on the* observed indices for 0 05 0 1 0 2 0 5 1 0 and 2 0 Hz

Finally Hook s law

$$\varepsilon_t=\frac{1}{E}\left(\sigma_t-\frac{\sigma+\sigma_x}{m}\right)$$

provides the expression

$$E=\frac{\Delta\sigma_t-(1/m)\,\Delta\sigma_x-(1/m)\,\Delta\sigma}{\Delta\varepsilon_t}$$

E is the proposed *tonometric index* of the *myomet* rium It must be emphasized that *in this* connec tion *E* 1) *mirrors* the difference between conditions *before* and at maximal distension 2) is calculated from the appraisal of a section through the *rotation* ellipsoid assuming this to be part of a *cylinder* 3) pays regard only to the stresses in the innermost layer of the myometrium where stresses are maxi mal

It is evident from *the results* of the experimental study that one *index value* is characteristic only for *a specified frequency of* muscular excitation A se quence of tonometric *indices* may therefore be *plotted* versus frequency in coordinate *systems* (Fig 4) When indices relating to one individual *are* used to evaluate myometrial effects of *pharmaco* logically active agents the line of the *regression of* the index values on the *logarithm with* base 10 of frequency is calculated utilizing the *observations* for frequencies within the range 0 05–2 Hz *Thereby* the *regression line* is formed firstly for the individual $y=a+bx$ and secondly for a group of individuals ac cording to the equation $y=y_1-b_1x_1+b_1x$ (Fig 5)

DISCUSSION

Three basic properties characterize the act... smooth muscle tonus *adaptability and* ... tility Various arrangements *have been used for* re*cording these* qualities of the muscular wall of hol*low* organs in vivo The results are generally diffi*cult* to comprehend except for the dynamics of the *thin* wall of the urinary bladder For this organ the convenience of monitoring slow alterations ... stress relaxation accompanying step-wise change ... volume has bridged the gap between conventional *cystometry and* the analysis of the elastic and vis*cous* properties of the bladder wall (2 1? 18 ... contrast investigation of the mechanical behav... of the uterine wall in vivo has been hampered by the difficulty of using monitoring techniques that al*low* exact determination of the volume-press... relationship (3 4 5 6 10 11 15) Development ... the field of uterine dynamics might be promoted by the application *in vivo* of methods introduced ... *the* study of specific aspects of the *excit* ... *contraction* coupling mechanism such as the anal*ysis* of length tension diagrams (8) force veloc... parameters (17) and stress response to sinusoidal strain (1)

It became obvious during earlier *in vivo* studies ... the human uterus that the adaptation phenomena could be studied by step-wise distension of the or*gan* or by the use *of a slow* linearly increas... *stretch* However data obtained from techn... applying oscillatory changes in length are easier ... analyze This is because sinusoidal movements ... be realized with mechanical accuracy A diffic... remains in that the oscillations must be made ...

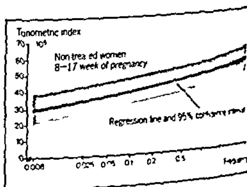


Fig 5 The line of regression of index values on fre... for the group ($n=$ 0) of non-treated pregnant women ... control series $y=47\ 4+8\ 2x$ The 95% confidence in... val is symmetrically distributed around the regression ...

le over a wide range of frequencies Mechanical mulation must be applied at a slow rate if one is analyze the relationship in phase between disten n and development of tension High frequencies e needed in order to study vibration induced re tation (13) With the present device there are oblems in ascertaining the exactness of operation the low (<0 01 Hz) as well as in the high (>4 Hz) quency ranges but for different reasons Me nical instability hinders the function of the bel is in the low range while hydrodynamic compli ions render the pressure measurement unreliable h frequencies At present these factors impede study of for example the effect upon the uter cervix of mechanical influences causing fast ef ement (18)

n the present investigation the response of the ine wall to mechanical and to pharmacological mulation has been recorded primarily as a varia n in intrauterine pressure It should be empha ed that the tonometric index defined with this erimental model and suggested as a measure of e effect is to be regarded as a synthetic discrimi or which although it has the dimension of an sticity module (stress/strain) does not imply any ple physical property of the uterine wall

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THE USE OF SALBUTAMOL IN OBSTETRICS

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ract Sympathomimetic amines have been used with aim of abolishing uterine contractions On the basis of lts from an in vivo technique for testing the specificity affinity of the beta₂-receptor stimulating agents lamol was used for a clinical trial Five case histories selected in order to illustrate the possibility of utiliz albutamol in emergency cases with the aim of achiev erine relaxation during the period of time between dmission of the patient and the commencement of ery by for example caesarean section

efficacy with which beta receptor adrenergic ts induce relaxation of smooth muscle has been mented and a wealth of literature is available his matter (4 9 2) A serious adverse side t however has been the influence of the drugs he $beta_1$ receptor mediated properties of cardiac tion especially the production of tachycardia the aim of avoiding this reaction which is etimes very unpleasant for the patient new ts have been developed during the last few s These drugs are characterized by more pro- nced specificity for the $beta_2$ receptors in oth muscle (5 3 1) Measurement of the relax effect upon the *pregnant* human uterus in vivo aled that the ratio between the effects on le and on heart was especially favorable for e of the new drugs e g salbutamol and fenote 6) In clinical trials salbutamol was also shown ostpone delivery in a high proportion of pa ts with premature contractions (8) The avail ty of agents capable of relaxing the uterine metrium would however be advantageous in cases of complications during labor at full t In this report the results of the treatment of cas s with salbutamol will be reported

METHODS

Pregnant women presenting themselves in emergency situations during labor were given salbutamol with the aim *of inducing uterine relaxation* Twenty five mg of the drug were added to 1000 ml 5% dextrose or 0 9% sodium chloride The infusion set using a Univac drip counter was connected to an indwelling catheter in the brachial vein Maternal systolic and diastolic blood pressures and heart rate were determined at intervals no longer than 15 min The fetal heart rate and the uterine contractions were recorded continuously with a Hewlett Packard or Corometric cardiotocograph The dosage of salbutamol was individually adjusted depending on maternal cardiovascular function and uterine activity within the range from 2 5 μg/min to 75 μg/min usually ? 5–22 5 μg/min

RESULTS

The results are given in the form of case histories Among a large series of patients studied 5 cases were selected for this presentation Data in general are given in Table I

Case I A M 2? years III gravida II para Admitted to the hospital at full term active labor for 10 h Temperature 39 0°C cervix 6 cm dilated membranes ruptured fetus in a transverse lie one shoulder impacted in the pelvic inlet the arm prolapsed Duration of contractions 45 sec intervals 2–3 min FHR record disclosed variable and late decelerations Caesarean section was decided upon With the aim of achieving uterine relaxation and relieving fetal asphyxia the presence of which was made highly probable by the late deceleration phenomena a salbutamol infusion was started at a dose of 1? 5 μg/min and increased to 37 5 μg/min The intervals between contractions increased and their amplitude decreased *The maternal heart rate rose* from 100 beats/min to 170 beats/min which necessitated a reduction of the dose of salbutamol Changes in systolic and diastolic blood pressure were minimal The infusion of salbutamol was continued until the baby was delivered through a lower segment incision The uterus was well relaxed and the infant easily extracted Birth weight was 3 8 kg Apgar score 7 at 1 min and 10 at 5 min

Table I *Details of patients*

Patient	Age	Gravity	Parity	History	Remarks
1 A M	22	III	II	2 normal deliveries 1 infant dead after 7 months	Transverse lie
2 M T	20	II	0	1 abortion	Twin constriction ring
3 S H	23	IV	II	1 normal delivery 1 stillborn 1 abortion	Abruptio placentae fetal distress
4 R W	2?	II	I	1 normal delivery	Fetal distress
5 M N	29	III	II	2 caesarean sections cephalopelvic disproportion	?7 week premature contractions

Case 2 M T 20 years II gravida 0 para Admitted in active labor with an undiagnosed twin pregnancy gestational age 37 weeks The first twin was delivered normally birth weight 1 5 kg Apgar score 10 at 10 min The second twin presented with an incomplete foot presentation The cord prolapsed the pulse rate in the cord was counted to be 60 beats/min Clinical signs indicated an abruption of the placenta Myometrial tension increased and a constriction ring formed at the junction between the upper and the lower segment of the uterus around the knee of the infant which was completely stuck Pure oxygen was given by mask and an i v infusion of salbutamol was started at a dose of 75 μg/min The constriction ring relaxed within 2 min after the initiation of the infusion and the fetus was easily extracted *Birth weight 1 7 kg Apgar* score 4 at 1 min and 7 at 10 min

Case 3 S H 23 years IV gravida II para Admitted during active labor membranes ruptured The amniotic fluid was thick and meconium stained The uterine size was similar to that of a 36-week pregnancy The fetus was in vertex position at station 0 The uterus was hypertonic cervix 100% effaced uterine os 3 cm dilated The fetal heart rate base line showed reduced beat-to-beat variability Early deceleration change was present with a reduction in heart rate amounting to more than 60 beats/min Change in maternal position together with oxygen administration had no influence on the FHR pattern salbutamol infusion was started at a dose of 25 μg/min The contractions stopped completely after 11 min. FHR became normal with reappearance of beat to-beat variation (Fig 1) A caesarean section was performed and an infant with a birth weight of ? ? kg was delivered. Apgar

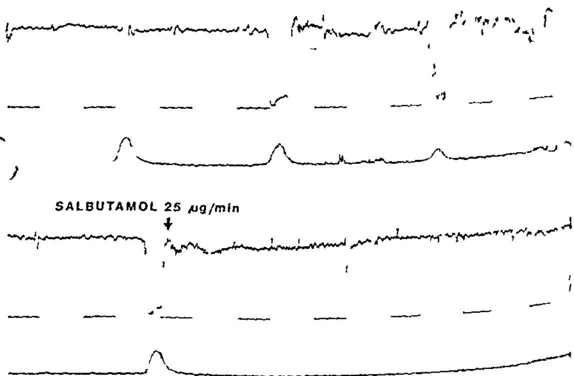


Fig 1 Salbutamol infusion in a case with abruptio placentae Deceleration and reduced beat to-beat variation

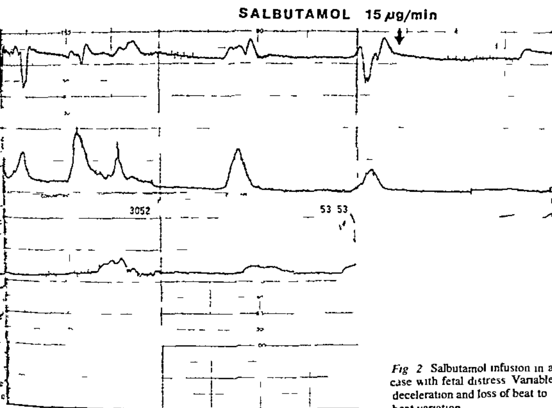


Fig 2 Salbutamol infusion in a case with fetal distress Variable deceleration and loss of beat to beat variation

...re 3 at 1 min and 7 at 5 min The placenta showed an ...on of one third of its area

...ase 4 R W ?? years II gravida I para Admitted ...th prolonged labor membranes ruptured FHR showed ...beat to-beat variability and so-called variable decel...ations occurred (Fig 2) A caesarean section was ...nned a salbutamol infusion in the dosage of 15 µg/...n was started Uterine contractions ceased completely ...ter 3 min The FHR pattern which was monitored up ...til delivery continued however to show loss of beat ...-beat variation Birth weight 4 1 kg Apgar score 6 at ...min and 10 at 7 min

Case 5 M N ?9 years III gravida II para Admitted ...the ??th week of pregnancy because of premature ...ine contractions which were regular cervix was not ...aced uterine os closed Two earlier caesarean sections ...e to cephalopelvic disproportion A salbutamol infusion ...s started at a dose of 1? 5 µg/min and increased to 25 ...min after 15 min Uterine contra tions disappeared ...mpletely Salbutamol was continued with oral adminis...ation at a dose of ? mg×4 The pregnancy continued ...turbed

DISCUSSION

...e sympathetic action of adrenergic agonists is ...aracterized in terms of alpha and beta receptor ...ediated responses each possessing different re...ceptors Th beta receptors are further subdivided into beta₁ receptors within the heart with chronotropic and inotropic effects and $beta_2$ receptors in smooth muscles with relaxing properties In addition the release of cyclic AMP induces general effects on carbohydrate and lipid metabolism

Even though adrenergic agonists employed with the aim of arresting uterine contractions have been free from alpha receptor stimulating properties they have had a mixed $beta_1$ and beta receptor affinity The widening of pulse amplitude and some times a resultant decrease in mean blood pressure were not infrequently severe enough to prevent further use of the drug Efforts were made to abolish the side effects by the use of simultaneously administered beta receptor blocking agents However such an action was neither supported by theoretical considerations nor was it sufficiently successful in its practical application

Pharmacological research made possible the synthesis of agents with more selective $beta_2$ receptor affinity and several such agents have been marketed In the literature reports are available presenting results of experiments regarding the

Table I *Details of patients*

Patient	Age	Gravity	Parity	History	Remarks
1 A M	22	III	II	2 normal deliveries 1 infant dead after 7 months	Transverse lie
2 M T	20	II	0	1 abortion	Twin constrictor ring
3 S H	23	IV	II	1 normal delivery 1 stillborn 1 abortion	Abruptio placenta, fe[illegible] distress
4 R W	22	II	I	1 normal delivery	Fetal distress
5 M N	29	III	II	2 caesarean sections cephalopelvic disproportion	[illegible]7 week premature con tractions

Case 2 M T 20 years II gravida 0 para Admitted in active labor with an undiagnosed twin pregnancy gestational age 37 weeks The first twin was delivered normally birth weight 1 5 kg Apgar score 10 at 10 min The second twin presented with an incomplete foot presentation The cord prolapsed the pulse rate in the cord was counted to be 60 beats/min Clinical signs indicated an abruption of the placenta Myometrial tension increased and a constriction ring formed at the junction between the upper and the lower segment of the uterus around the knee of the infant which was completely stuck Pure oxygen was given by mask and an i v infusion of salbutamol was started at a dose of 75 μg/min The constriction ring relaxed within 2 min after the initiation of the infusion and the fetus was easily extracted Birth weight 1 7 kg Apgar score 4 at 1 min and 7 at 10 min

Case 3 S H 23 years IV gravida II para [illegible] during active labor membranes ruptured The [illegible] fluid was thick and meconium stained The [illegible] was similar to that of a 36-week pregnancy The fetus [illegible] in vertex position at station 0 The uterus was [illegible] cervix 100% effaced uterine os 3 cm dilated The [illegible] heart rate base line showed reduced beat to-beat [illegible]ty Early deceleration change was present with a [illegible]tion in heart rate amounting to more than 60 beats [illegible] Change in maternal position together with [illegible] administration had no influence on the FHR [illegible] salbutamol infusion was started at a dose of [illegible] The contractions stopped completely after 11 [illegible] [illegible] became normal with reappearance of beat to-beat [illegible]tion (Fig 1) A caesarean section was performed [illegible] infant with a birth weight of [illegible] kg was delivered [illegible]

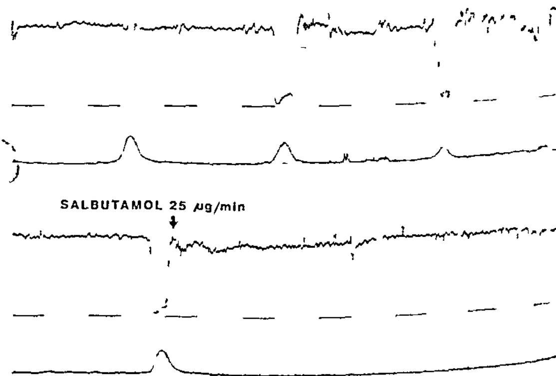


Fig 1 Salbutamol infusion in a case with abruptio placentae Deceleration and reduced beat to-beat variation

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STUDIES ON THE MODE OF ACTION OF CLOMIPHENE CITRATE

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bstract In order to further investigate the mode of ac tion of clomiphene citrate 5 oophorectomized women in e age range 28 to 41 years were followed with weekly eterminations of serum FSH and LH for 20 weeks after e operation They received no treatment during the first weeks but during the next 16 weeks they were given tradiol 2 mg×2 daily orally and from the 12th to the th week in addition clomiphene citrate 50 mg×2 daily he high level of FSH after the oophorectomy decreased adually during the treatment with estradiol alone but is effect was partly neutralized by clomiphene citrate as e observed a significant increase in FSH within 1 week initiating treatment with clomiphene citrate On the her hand we did not find any significant changes in FSH thin 4 weeks after treatment with clomiphene citrate as discontinued The high level of LH after oophorec my did not show any significant changes during the hole treatment period. It is concluded that clomiphene rate primarily stimulated FSH secretion most probably a competition with estradiol for the receptor sites in the pothalamus or the pituitary In addition it is concluded at clomiphene citrate has a prolonged effect probably ecause of a tight binding to the receptor sites

nce Greenblatt (6) first observed that clomiphene rate could induce ovulation in a high percentage f anovulatory women this treatment has been idely used for induction of ovulation in sterile omen (3 8 12 14 15 16 26) Nevertheless the ode of action of clomiphene citrate on the human eproductive system is still not quite clarified

Two principal theories concerning the action of lomiphene citrate have been proposed The first heory claims that clomiphene citrate acts on the hypothalamic pituitary system It is believed that clomiphene citrate or rather the *cis* isomer of the molecule (2 7 29) blocks the receptor sites in the hypothalamus or the pituitary in competition with estradiol thus causing an increased gonadotropin secretion (11 21) This theory is in agreement with the investigation by Eisenfeld & Axelrod (5) and Roy et al (22) who found a decreased ³H-estradiol uptake in the hypothalamus and the pituitary in rats treated with clomiphene citrate compared with con trol animals

The second theory indicates a direct action of clomiphene citrate on the biosynthesis of steroids in for instance the ovary and the placenta Some investigators (9 24 25) have observed that clomi phene citrate causes an increased conversion of testosterone to estradiol in placenta microsomes *in vitro* This effect was due to an inhibition of the nicotineamide adenine dinucleotide phosphate (NADPH) cytochrome *c*-oxido reductase system with a subsequent availability of NADPH which is an obligatory co factor for aromatization of the A ring Other investigators have in *in vitro* experi ments shown that clomiphene citrate stimulates the 3β-ol-dehydrogenase Δ^5 isomerase in human corpora lutea slices (10) and 17β-ol dehydrogenase in fungus homogenates (1) Both enzymes together with NADPH are necessary for the steroid trans formation and it appears from these *in vitro* in vestigations that clomiphene citrate stimulates im portant steps in the estrogen biosynthesis

The aim of the present study was further to eluci date the effect of clomiphene citrate on the hypothalamic pituitary system

MATERIAL AND METHODS

The material consists of 5 women aged 28 to 41 who were bilaterally oophorectomized because of various gyneco logical diseases but it should be noted that none of the women showed any signs of estrogen deficiency before

pharmacological properties and the order of pre cedence of specificity of one and the same agent for the beta, and beta receptors respectively The effect on bronchial muscle is quantitatively evaluated from in vitro and in vivo experiments while the action on uterine smooth muscle most often has been described from in vitro studies only Recently an in vivo technique for the quantitative evaluation of the effect upon the pregnant uterus has been presented (6) It was demonstrated that salbutamol and feneterol were the most potent agents among the $beta_2$ receptor stimulating agents with respect to uterine relaxation

In all of the studied cases salbutamol had a dramatic effect on uterine activity Most often uterine contractions were completely abolished this even in cases with ruptured membranes and fully dilated cervices The influence upon the resting pressure could not be determined because only external tocometry was employed The influence upon maternal systolic blood pressure was negligible while the diastolic pressure usually decreased sometimes by as much as 25–50% The influence upon diastolic pressure was however both dose dependent and subjected to pronounced interindividual variation The same was true regarding the effects on maternal heart rate

The influence upon FHR of infusions of salbutamol to the mother was inconsistent most often changes in heart rate could not be detected The late deceleration pattern accepted as a sign of fetal asphyxia is evidently not provoked as soon as intrauterine contractions are inhibited The disappearance of the late deceleration pattern can there re not be utilized as a parameter of change in fetal l being Beat to beat variations detectable in ependent of uterine activity can be suggested as a more useful parameter for the study of the effect of salbutamol on the oxygen supply to the fetus This suggestion is valid provided analgesic drugs have not been administered to the mother in large quantities This series did not include enough patients to allow an analysis of the reappearance of beat to-beat variation following the administration of salbutamol

In the literature data have accumulated about the beneficial effect upon the fetus of an infusion to the mother of sympathomimetic amines Experimental work with subhuman primates has indicated that the infusion of isoproterenol which is a beta, and beta receptor stimulating agent causes a decrease in arterial fetal PO_2 (7) This finding might be d [illegible] the fact that maternal cardiovascular function was affected to a major degree but it might also be ascribed to the situation of using animals [illegible] anaesthesia for the investigation This [illegible] makes it uncertain whether the results are appl[illegible]ble in human clinical obstetrics Besides these [illegible]planations offered above there are reasons to believe that the relaxation of smooth muscle with increased conductance in some vascular [illegible] can produce a partial redistribution of blood [illegible] from the visceral to the systemic circulation Further studies are necessary and have been [illegible]tiated for the elucidation of these mechanisms [illegible] humans

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trate in the above mentioned doses Within one eek the mean value of serum FSH had increased om 100 mIU/ml to 145 mIU/ml and this level of SH was maintained during the following 3 weeks he increase in serum FSH was significant $p<0.01$) It should however be noted that the high r treatment level of FSH was never reached After e treatment with clomiphene citrate was dis ontinued a slight decrease in serum FSH was seen ut the fall was not significant within the 4 weeks of bservation

Fig 2 shows in the same way the changes in the erum LH level in the 5 women during the 20 weeks f observation It appears that 2 weeks after the ophorectomy the serum LH values are within the ange for postmenopausal women and the serum H level did not show any significant changes uring the remaining part of the observation period

Clinically it was characteristic of all 5 women that ey had climacteric complaints (hot flushes sweat gs headache) within the first 4 weeks after the ophorectomy These symptoms disappeared com letely during the treatment with estradiol alone but thin one week after treatment with clomiphene trate was initiated all 5 women again had the me complaints to a certain degree and the symp ms increased during the next 3 weeks After eatment with clomiphene citrate was dis ntinued the climacteric complaints decreased t very slowly and one out of the 5 women had ll symptoms 4 weeks after the last tablet of miphene citrate had been taken

DISCUSSION

he present investigation confirms that clomiphene trate undoubtedly has a central effect on the hypo alamic pituitary system It seems as if clomiphene trat primarily stimulated the secretion of FSH hereas we did not observe any significant stimula ion of th LH secretion as reported by several ther inve tigators (11 13 19 28 29) It should owever be noted that one out of 5 women in our udy showed a significant increase in both serum FSH and LH The observed variation in the LH esponse to clomiphene citrate might be explained y 1) different preparations and doses of the e ogens used 2) the presence or absence of varies in the women investigated and 3) different uration of the t eatment with clomiphene citrate

The level of estrogens seems to be of decisive importance for the gonadotropin response to treat ment with clomiphene citrate Thompson & Mel linger (28) showed in a patient with Turner s syndrome who did not receive any substitution therapy with estrogens that clomiphene citrate did not alter the urinary excretion of FSH and LH at all The same patient was then treated with diethyl stilbestrol until the excretion of gonadotropins was significantly suppressed and repeated stimulation with clomiphene citrate during continued treatment with estrogen now caused a significant increase in the excretion of both FSH and LH They concluded therefore that a certain estrogen level is necessary for clomiphene citrate to stimulate the secretion of gonadotropins On the other hand Thompson et al (27) found a marked suppressive effect of estradiol benzoate on the LH response to exogenous luteiniz ing hormone releasing hormone when the concen tration of estradiol was in the range of 400–1 000 pg/ml serum and a similar suppression was observed by Pedersen et al (20) when the patients received a daily dose of 2 mg estradiol+1 mg estriol

Another important observation is that clomi phene citrate seems to exert an effect for several weeks as we did not observe any significant de crease in the FSH level within the first 4 weeks after the treatment with clomiphene citrate was dis continued Our finding is in good agreement with the observation reported by Schreiber et al (23) who after administration of ^{14}C labelled clomiphene citrate found that even if 51% of this drug was eliminated within 5 days they could still detect small amounts of ^{14}C labelled clomiphene citrate in the patients 6 weeks later This prolonged effect is probably due to a tight binding of clomiphene citrate to the receptor sites in the hypothalamus or the pituitary

Furthermore we would like to add that our observations indicate that FSH and LH in women to a wide extent are regulated independent to each other Since only one gonadotropin releasing hormone has been found so far the mechanism of this regulation is at present obscure

Several *in vitro* experiments (1 9 10 24 25) indicate that clomiphene citrate in addition to the central effect on the hypothalamic pituitary system also might have an effect directly on the ovary but a similar effect *in vivo* has not yet been found

Crooke et al (4) have however in 6 amenorrheic women observed that clomiphene citrate aug

mented the effect of exogenous FSH by a factor of 173 % as shown by the excretion of estrogens This finding might be explained by a direct effect of clomiphene citrate on the ovary

ACKNOWLEDGEMENT

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THE BEHAVIOUR OF MICROSOMAL MONO ELECTRON CARRIERS IN HUMAN PLACENTA DURING LATE PREGNANCY

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bstract The activities and the content of enzymes in ..ed in mixed function oxidase *systems (cytochromes* -450 and b_5 NADPH-cytochrome *c* reductase and ADH cytochrome *b* reductase) in microsomes from 114 ..man placentae were found to increase from the 34th up the 38th–39th week of gestation and later to decrease ..til the 43rd week Such a process can be related to the ..llowing (i) the phospholipid content of microsomal ..embranes (ii) the protein synthesis possibly induced by ..eroids such as androstenedione and testosterone

..e function currently assigned to the placenta as a ..hly active organ suggests that it might metabo-.. foreign compounds introduced by the mother ..s acting as a protective barrier for the fetus or at ..ast as a substitute organ for the metabolism of ..ch compounds with respect to both maternal and ..tal liver During the transport from maternal to ..al circulation foreign compounds such as drugs .. chemical additives cross the placenta simply by ..fusion (11)

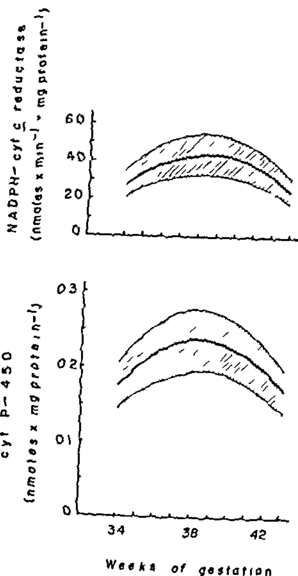
The enzymatic systems in liver and placenta me..bolizing most foreign compounds are termed ..xed function oxidases (27) or monooxygenases (..) and consist of cytochrome P-450 which is ..e terminal oxidase another hemoprotein (cyto..chrome b_5) and two flavoproteins (NADPH cyto..chrome *c* reductase and NADH cytochrome b_5 re..ductase) The occurrence of cytochrome P-450 in ..man placenta was reported by Meigs and Ryan (29) at term and by Juchau et al (17) in the early ..ges of gestation This hemoprotein is mostly ..nd in syncytiotrophoblast together with cyto..chrome b_5 and the flavoprotein NADPH-cyto..chrome *c* reductase (32) As for rat live micro..somes cytochrome P-450 spectra with different substrates and ligands have been obtained in microsomes of human placenta and some differences in this respect between the two types of microsomal preparations have been described (17 32)

The lack of data concerning the activities and content of enzymes of the mixed function oxidase systems in the course of gestation has prompted us to investigate this subject in order to determine whether the metabolizing capacity of the placenta with respect to some drugs changes according to the time of gestation The results show increasing con tent and activity of these enzymes from the 34th until the 38th–39th week of gestation and after that a decline from the 39th to the 43rd week

MATERIALS AND METHODS

The microsomal fraction was obtained according to Om ura & Sato (35) from 114 human placentae between the 34th and the 43rd week of gestation after spontaneous delivery or Cesarean section The placentae were im mediately taken and poured into 0 15 M KCl containing 50 mM Tris HCl buffer pH 7 5 at 0–4 C after removal of membranes and umbilical cord The microsomal fraction was suspended in the medium described above yielding a protein concentration of about 20 mg/ml Proteins were determined by the biuret method (24)

Difference absorption spectra were obtained in a dual wavelength/split beam Aminco Chance spectrophotome ter Cytochrome *b* was measured from the NADPH dif ference spectrum of the CO-treated microsomes using $\Delta\epsilon$ (424–409 nm)=165 cm^{-1} mM^{-1} (10) Cytochrome P-450 was measured from the NADPH *plus* dithionite difference spectrum of CO treated microsomes using $\Delta\epsilon$ (450–490 nm)=91 cm^{-1} mM^{-1} (22) This method required base line determination with both cuvettes already saturated with CO which allowed us to determine cytochrome P-450 irrespective of hemoglobin contamination Because o peculiar spongy structure placenta is quite rich i



1 Kinetics of microsomal cytochrome P-450 and ADPH-cytochrome c reductase of *human placenta* The tochrome content and enzyme activity *have been esti*mated at *different stages* of *pregnancy* in the microsomal *fractions* as described under Materials and Methods Placentae *were tested* weekly from the 34th to the 43rd week of gestation *and each value is the* mean of *7–14* experiments The curves were obtained *from a II degree poly*nomial correlation by the least squares method

and hemoglobin can be hardly removed *during microsomal* isolation NADPH cytochrome *c* reductase was *measured following* cytochrome c reduction at 546 nm in the presence of NADPH (4?) NADPH-cyto*chrome b₅* reductase was measured following NADH *oxidation* at 340 nm in the presence of potassium ferricyanide as electron acceptor (38) A Honeywell computer was used for data processing

RESULTS

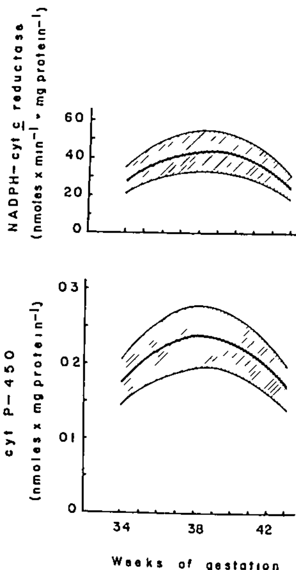
All the four enzymes were found to increase fro the 34th to the 38th week of gestation and to de crease from the 38th–39th to the 43rd week of gesta tion (Figs 1 and 2)

The levels of microsomal enzymes as a functi of time result from a II degree correlation acc ing to the minimum square method

DISCUSSION

The most striking feature is the similarity be an the pattern of enzyme activities and cytochro contents The fact that the four enzymes in t placenta behave similarly is a further evidence the hypothesis that they are closely related and a indispensable for oxidation reactions at microso level as suggested by Hildebrandt & Estabro (14) and by Mannering et al (?6) for liver tissue

As the placenta goes rapidly towards ma ura and ageing it can be assumed that the time cou of the four enzymes biochemically reflects what currently termed placental ageing" Seve studies have emphasized an increase in microso oxidative enzymes and a variation of oxida capacities with respect to drugs in rat liver t during the early stages of growth of the an (7 18 20 37) On the other hand a decre in NADPH cytochrome c reductase activi y a NADPH nitrotetrazolium reductase activ ty as w as in the cytochrome P-450 content was fund occur in old rats as compared to young or (12 21) Such changes could be related to modifica tions in the phospholipid content of microso membranes Experiments *in vitro* have mde demonstrated that phospholipase D brings ab an inactivation of liver microsomal NADH cy chrome c reductase (25) Furthermore phosph content of rabbit placenta has been found to sha increase as gestation proceeds (1) Hen e two p sible causes for the variation in phospholipid co tent of human placenta during gestation may postulated (i) changes in endogenous pho pase activity (ii) changes in the extent of lip oxidation It has been demonstrated that de crease in respiratory control in aged rat liver chondria is partly related to the activa on of e genous phospholipases *(16) The presence* of phospholipases was also demonstrated at the mic mal level (33) Moreover it has been pos le an increase in lipid peroxidation could res



1 Kinetics of microsomal cytochrome P-450 and NADPH-cytochrome c reductase of human placenta The cytochrome content and enzyme activity have been estimated at different stages of pregnancy in the microsomal fractions as described under Materials and Methods Placentae were tested weekly from the 34th to the 43rd week of gestation and each value is the mean of 7–14 experiments The curves were obtained from a II degree polynomial correlation by the least squares method

and hemoglobin can be hardly removed during microsomal isolation NADPH cytochrome c reductase was measured following cytochrome c reduction at 546 nm in the presence of NADPH (4) NADPH-cytochrome b_5 reductase was measured following NADH oxidation at 340 nm in the presence of potassium ferricyanide as electron acceptor (38) A Honeywell computer was used for data processing

RESULTS

All the four enzymes were found to increase from the 34th to the 38th week of gestation and to decrease from the 38th–39th to the 43rd week of gestation (Figs 1 and 2)

The levels of microsomal enzymes as a function of time result from a II degree correlation according to the minimum square method

DISCUSSION

The most striking feature is the similarity between the pattern of enzyme activities and cytochrome contents The fact that the four enzymes in the placenta behave similarly is a further evidence of the hypothesis that they are closely related and indispensable for oxidation reactions at microsomal level as suggested by Hildebrandt & Estabrook (14) and by Mannering et al (26) for liver tissue

As the placenta goes rapidly towards maturation and ageing it can be assumed that the time course of the four enzymes biochemically reflects what is currently termed placental ageing Several studies have emphasized an increase in microsomal oxidative enzymes and a variation of oxidative capacities with respect to drugs in rat liver during the early stages of growth of the animal (7 18 20 37) On the other hand a decrease in NADPH cytochrome c reductase activity and NADPH nitrotetrazolium reductase activity as well as in the cytochrome P-450 content was found to occur in old rats as compared to young ones (12 21) Such changes could be related to modifications in the phospholipid content of microsomal membranes Experiments *in vitro* have indeed demonstrated that phospholipase D brings about an inactivation of liver microsomal NADH cytochrome c reductase (25) Furthermore phospholipid content of rabbit placenta has been found to sharply increase as gestation proceeds (1) Hence two possible causes for the variation in phospholipid content of human placenta during gestation may be postulated (i) changes in endogenous phospholipase activity (ii) changes in the extent of lipid peroxidation It has been demonstrated that the decrease in respiratory control in aged rat liver mitochondria is partly related to the activation of endogenous phospholipases (36) The presence of phospholipases was also demonstrated at the microsomal level (33) Moreover it has been postulated that an increase in lipid peroxidation could result

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HCT AND THYROID FUNCTION IN MOLAR PREGNANCY

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HCT TSH T3 T4 PBI T3 RSU TBG acity BMR and thyroid uptake of radioiodine ured simultaneously on the volunteers with m mole and normal pregnancy TRH stimula were performed on the two groups The serum s were higher in association with molar preg s in normal pregnancy TSH levels were within gnant range in the two groups T3 T4 PBI R and thyroid uptake of radioiodine suggested perfunction in molar pregnancy with a greater n that in normal pregnancy TBG binding capa T3-RSU were similar in the two groups The levels of TRH stimulation tests ranged widely s with molar pregnancies but were within the nt range in the subjects with normal pregnan- e findings suggest thyroid hyperfunction in the gnancy is due to a larger amount of HCT than pregnancy

al suggested in 1955 that a thyroid stimu bstance may exist in the human placenta r a purified protein with TSH activity was ed by Hennen et al (2) Hershman et al (3) highly purified glycoprotein with TSH acti- as extracted from human term placenta by sent authors (4 5) This protein hormone is human chorionic thyrotropin (HCT) and we ed on its biological biochemical and im logical characters in 1972 (4 5) We demon- d that the serum HCT level estimated with adioimmunoassay using ^{131}I HCT and anti- serum increased progressively during preg y (6) and that the progressive elevation of thy function during pregnancy was due not to gen, but to HCT originating from the placenta

kkay (8) Singh (9) and Dowling (10) described changes of the serum protein binding iodine) thyroxine binding capacity (TBG binding city) thyroid uptake of radioiodine and con- ion ratio in patients with the molar pregnancy and found them similar to those in women with normal pregnancy but to a more extreme degree

Odell et al (11) using bioassay detected high TSH activity in the serum of patients with molar pregnancies Hershman et al extracted a thyroid stimulator from the chorionic tumour tissue and the serum of a patient with coexistent hyperthyroidism and hydatidiform mole this they called molar thyrotropin (12)

Recently we have detected large amounts of HCT in the serum of patients with molar pregnancies by radioimmunoassay using ^{131} HCT and anti HCT serum (6) and suggested that the HCT level was a useful indicator in the treatment of chorionic neoplasm (13)

In this paper the serum HCT levels and pituitary thyroid function in patients with hydatidiform mole and those with normal pregnancy are compared

SUBJECTS AND INVESTIGATIONS

HCT thyroidstimulating hormone (TSH) triiodo- thyronine (T3) thyroxine (T4) PBI effective thyroxine ratio (ETR) ^{131}I-triiodothyronine resin sponge uptake (T3-RSU) TBG binding capacity basal metabolic rate (BMR) and thyroid uptake of radioiodine were measured simultaneously in 30 patients with hydatidiform mole and all but thyroid uptake of radioiodine were done in 40 normal pregnant women at an early stage of gestation (week 8–15) Thyrotropinreleasing hormone (TRH) stimulation tests were performed in 30 patients with hydatidiform mole and in 20 women in early pregnancy

The serum HCT level was determined by a radioimmunoassay using $^{1[illegible]}$ I-HCT and anti-HCT serum reported previously (6) The serum TSH level and the serum T3 level were determined by radioimmunoassay using kits of Daiichi Radioisotope Laboratories (Tokyo Japan) The serum T4 and ETR were measured with Res-O-Mat T4 kit and Res-O-Mat ETR kit of Mallinckrodt Corporation (USA) The serum PBI level was determined with an auto analyzer technique and BMR was determined with the

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TUBAL STERILIZATION

With Special Reference to Electrocoagulation through the Laparoscope

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tract In the past 5 years 1 168 tubal sterilizations have en performed One thousand and twelve of these were formed by dividing the tube by diathermy through the aroscope Since the first cases and with increasing perience complications have been infrequent at the ut a slight bleeding from the mesosalpinx So far we we had ten failures probably due to lack of experience every failure it was found at re-examination that the e had not been divided—at least at one side The thod is quick and simple The patient suffers little in nvenience has a very small scar and is in hospital only short time It has been used in post partum cases but not suitable for patients who have had several ab minal operations

e frequency of legal abortions has increased in ny countries in recent years Unwanted pregnan s appear to be more common than before in te of improved methods of contraception

Many couples feel that older methods of con ception are no longer acceptable once they have perienced the simplicity of the pill On the other nd many women are able to take the pill only for limited time and others have been scared by re rts of various complications The intra uterine contraceptive devices also produce side effects d will have a relatively low acceptability rate

A practical alternative for many couples will then sterilization of one partner When they have all children they want and have decided on per manent contraception sterilization may be con dered

Many methods have been employed in the past the purpose of tubal sterilization The Madlener ration (7) or the modification of Pomeroy is bably the most frequently accepted method er possibilities are total salpingectomy Al drige s temporary procedure and cornual excision of the uterus

Post partum sterilization has been the method of choice in many hospitals A small incision gives ready access to the tube 2–3 days post partum As early as 1932 Skajaa (11) reported the first series of 126 cases of post partum sterilization from Oslo University Hospital In 1939 Amundsen (1) pre sented an additional 150 cases Blom Hartvigsen (4) carried out a survey of 267 new cases from the same hospital in 1951 The combined series of 543 cases were complicated by 18 cases of thrombosis and 1 severe infection The mortality rate was 0 18% No failures were mentioned In 1957 Jensen & Lester (5) published a series of 734 cases of sterili zation by the Madlener operation from Denmark There were two deaths but no other major com plications

A sterilization method should be easy with minimal risk to the patient It should be as effective as possible and should not carry any side effects In 1937 Anderson (2) suggested the possibility of tubal cauterization during peritoneoscopy Power & Barnes (10) in Michigan had the same idea but none of them have published reports of patients treated in this way

With improved equipment and the fiberoptic light laparoscopy has gained in popularity in recent years Palmer (8) and Steptoe (12) introduced a new improved laparoscope with fiberoptic light and surgical equipment for different procedures A simple method of tubal electrocoagulation under laparoscopic control was presented

Following the initial presentations by Palmer and by Steptoe many investigators have used their methods unaltered or partly modified and several

Table I *Survey of the series*

	No of patients					
	1970	1971	1972	1973	1974	Total
Resect Pomeroy	73	40	19	14	10	156
Palmer	76	175	186	258	317	1 012
Total	149	215	205	272	327	1 168

series have been published Steptoe had one failure in 310 cases No complications were described Svennerud & Åstedt (13) in Sweden presented a series of 42 cases in 1968 Listen et al (6) published a series of 760 patients sterilized by laparoscopy Nine became pregnant after the operation but only 4 were found to be operative failures Six patients required laparotomy to control bleeding

Cohen Taylor & Kass (3) reported a series of 50 cases treated with a slightly different technique which allowed histological verification of tubal tissue They had no failures and no complications followed

Peterson & Behrman (9) recently published a series of 186 women sterilized by electrocoagulation and cutting of the tubes One pregnancy occurred while 5 patients required laparotomy to control bleeding *Perforation of the stomach occurred once* and in 5 patients the uterus was perforated by the instrument inserted to manipulate the organ

Wheeless (14) from experience in 75 patients advocated the method as an excellent procedure for sterilization in the out patient department In series hemorrhage occurred in 3 patients one of om *required laparotomy One* patient had post operative aspiration pneumonia The observation time was too short to decide on failures

Pomeroy s tubal resection has previously been the method of choice for sterilization in our department During the last 5 years however this method

Table II *Age distribution*

Age	Number
20–24	30
25–29	189
30–34	335
35–39	384
40–44	212
45–49	18
Total	1 168

Table III *Tubal sterili ation Time of operation*

	At legal abortion	1 5 post partum day	Interval operation	Total
Resect Pomeroy	63	59	34	1[illegible]
Palmer	487	113	41[illegible]	1 0[illegible]
Total	550	17[illegible]	446	1[illegible]

has gradually been replaced by tubal electrocoagulation under laparoscopic control In patients [illegible] have had a number of laparotomies and [illegible] tensive adhesions can be expected we still [illegible] laparotomy if we do not succeed at once

MATERIAL AND METHODS

The present paper deals with a series of 1168 pat[illegible] sterilized at the Department of Gynecology Aker H[illegible]tal from 1970 through 1974 Of these 156 were trea[illegible]

Table IV *Medical indications for sterilization* [illegible]

Psychoneurosis	19
Sectio caesarea 2–4 times previously	13
Pre-eclampsia	6
Polyarthritis	4
Osteochondrosis columnae	1
Mb Bechterew	4
Ischias	4
Pelvic relaxation	5
Rhesus immunization	1
Tuberculosis	1
Lupus erythem Diss	1
Boeck s sarcoid	[illegible]
Hyperthyreosis	[illegible]
Hypothyreosis	3
Diabetes mellitus	5
Morbus renis	4
Hypertension	1
Asthma bronchiale	1
Hemophili carrier	[illegible]
Ca cerv ut st 0	1
Chondrodystrophia	[illegible]
Colitus ulcerosa	[illegible]
Cephalalgia atypical EEG	3
Seq Poliomyelitidis	1
Subileus	1
Hab postpartum bleeding	4
Cancer mammae op	[illegible]
Glaucoma	1
Prolapsus gen op	1
Hernia diaphragmatica	3
Paresis	[illegible]
Mb cordis	1
Epilepsia	5
Abortus habitualis	1
Hyperemesis	3
Advanced age	1
Earlier malformed children	[illegible]

Table V *Deliveries prior to sterilization*

Children	1970	1971	1972	1973	1974	Total
None	8	4	3	17	4	36
	40	76	74	124	158	47_
-4	90	1 6	1 0	116	151	603
or more	11	9	8	15	14	57
otal	149	215	205	272	327	1 168

Table VII *Therapeutic abortions prior to sterilization*

Therapeutic abortions	1970	1971	1972	1973	1974	Total
One	19	_6	31	51	55	18?
Two	6	4	6	8	19	43
Three or more	0	1	1	4	1	7
Total	25	31	38	63	75	232

...meroy's method while 1012 were treated by electrocoagulation during laparoscopy (Table I) The table also shows the increasing tendency to prefer the laparoscopic method in recent years

Table II shows the distribution by age The operation is performed most frequently on patients between 30 and 40 years but not less than 219 patients were below the age of 30 years

Table III shows the circumstances under which the operations were done About half of the operations were done in connection with legal abortions under the same anesthetic while 113 patients underwent post partum sterilization by the laparoscopic technique More recently we have with increasing experience preferred the latter method also post partum

The indications for the operation fell mainly into two groups The medical indications for the operation are seen in Table IV The other 1053 patients all had their application approved by the Department of Public Health

It appears from Table V that most of the women had children before they resorted to sterilization Thirty of the patients had had no pregnancy at all and some of the operations were performed on psychiatric indications About 30% of the patients had one or more spontaneous abortions before they were sterilized This is more than double the rate expected in the population (Table VI)

It is seen from Table VII that 20% of the patients had one or more therapeutic abortions before they were sterilized As previously shown in Table III about half of the sterilizations are performed at the time of therapeutic abortion These abortions are not included in Table VII

For laparoscopic sterilization *the following items of equipment are used* (i) Wolf Operating Laparoscope model Jacobs Palmer with angled optics (ii) Biopsy forceps and grasping forceps with blunt jaws and insulated shaft suitable for electrocoagulation (iii) Verre s needle for laparocentesis and insufflation Long Hegar dilator for manipulation of the uterus Wolf CO_2—PneuAutomatic chamber for CO_2 insufflation with control of volume and pressure (iv) Fiberoptic light source and cables

The anesthetic is chosen with regard to the risk of explosion and all operations were done under intubation anesthesia The patient is placed in 20–30 degrees Trendelenburg position and _–3 litres of CO_2 are insufflated to make a pneumoperitoneum The laparoscope is inserted through an incision in the lower edge of the umbilicus and with the grasping forceps the tubes are lifted away from other structures especially the intestines The tubes then are coagulated and divided 1–2 cm from the uterine cornu (Figs 2–3)

Table VI *Spontaneous abortions prior to sterilization*

Spontaneous abortions	1970	1971	1972	1973	1974	Total
	22	36	47	55	79	239
	7	10	13	14	17	61
ee or more	11	7	6	5	13	4
	40	53	66	74	109	342

Complications

At the very beginning we had some difficulty in making the pneumoperitoneum which is essential for this technique and we had three times to resort to laparotomy due to this technical failure Before we became familiar with the method we also had some cases with bleeding from vessels in the mesosalpinx Usually this bleeding can be stopped by electrocoagulation but in ?0 cases we had to undertake laparotomy to stop the bleeding which however was not severe in any case In our series we had *three severe complications A 26-year-old woman came* to the hospital 10 days after laparoscopic sterilization with diffuse peritonitis due to a lesion in the rectum This particular patient was at the time treated with corticosteroids for disseminated lupus erythematosus and we think that either this disease or the treatment might have been contributory to the complication *Two* other patients had a lesion of the intestine one followed by peritonitis These complications warned us to stay well away from other structures while doing the electrocoagulation

RESULTS

Despite the above mentioned complications our experiences with the laparoscopic method for tubal sterilization are good One of the greatest advantages *of the operation is the short hospital stay* (Table VIII) Most of the patients left the hospital on the first or second postoperative day and when discharge was postponed it usually was due to intervening holidays the patients wishes

Table VIII *Hospital stay after operation*

	Days after operation						
	1	2	3	4	5	6	7 (or more)
Laparoscopic sterilization (Palmer)	449	325	165	32	14	5	2
Resectio tubarum A M Pomeroy				5	7	1[illegible]	13[illegible]

Table IX *Failures*

Year	Name	Pregnant after (months)	At laparoscopic re sterilization found
1971	M S L	14	Right tube not coagulated
1971	G H	12	Right tube not coagulated
1971	K E	21	Right tube not coagulated
1972	L R	18	Right ligamentum rotundum divided
1972	A L E	9	Left tube not divided
1972	K J	3	Right tube not divided
1972	L H	8	Left tube not divided
1972	A M L	12	Left tube appeared normal
1973	B B	18	Right tube not divided
1973	B H	12	Right ligamentum rotundum divided

diseases being treated at the same time The time in hospital is now seldom more than 48 hours and can still be reduced if necessary Another great advantage of the operation is the almost complete absence of postoperative trouble often seen after laparotomy The patients usually feel only a dull ache in the back or on top of the shoulders due to some CO_2 that has not been evacuated The unsightly scar both outside and inside the abdomen resulting from laparoscopy places diathermy in a [illegible]rable light

In order to assess the efficiency of the method fully our observation time is rather short but our patients have been observed from 6 months to 5 years So far we have had ten failures probably due to lack of experience (Table IX) In 2 cases the mesosalpinx had been burned on one side only while in 4 other cases one tube had not been completely divided but partly coagulated leaving a narrow communication between the two ends In 2 cases the round ligament on one side had been burned and in 2 cases the tube appeared normal and no sign could be seen of the sterilization procedure

Initially we planned to carry out an X ray control of the patients or at least Levin s test postoperatively but we changed this decision because of the risk of reopening the tubal stump

CONCLUSION

With the laparoscopic method of tubal sterilization we have a relatively easy and rapid technique The contra indications to the operation are few [illegible] previously laparotomies where adhesions may [illegible] suspected In some cases we have done laparoscopies in spite of previous scars but never [illegible] extensive adhesions have been observed [illegible] earlier operations With increasing experience the operation is safe and secure and for the patient the inconvenience is the least possible

One advantage not mentioned in previous [illegible] on the subject may be the relatively long and [illegible] distal end of the tube This lateral end with [illegible] mal fimbriae might be a better tube to implant [illegible] uterus than the usually short end after Pomeroy sterilization and with better hope of [illegible] reversal of the sterilization

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lowered (2 12) or normal FSH levels (3 4) No relationship between the amount of bleeding during delivery and pituitary function could be found In the pathogenesis of Sheehan s syndrome the duration and severity of the shock is the most important and none of our patients had been in shock during delivery

The high LH level was due to HCG as verified in gel filtration study on Sephadex G 75 (Pharmacia Inc Sweden) The immuno-reactive LH was mostly (93%) eluted between serum albumins (mol weight 60000) and globulins (mol weight 200000) indicating a molecular weight between 60000 and 200000 The measured LH level represents HCG (mol weight 100000) which is not removed from the puerperal serum until two weeks post partum (13) rather than LH (mol weight 30000) The approximate true LH concentrations were 11 ng/ml before and 15 ng/ml after LRH stimulation These values are lower than our normal level of 20–40 ng/ml in healthy women during follicular phase

Our results further indicate that in the puerperium the LRH and TRH stimulation tests can be performed together as has been shown in normal subjects before (7)

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AMNIOTIC FLUID LECITHIN CONCENTRATIONS IN PREGNANCIES COMPLICATED BY HYPERTENSIVE DISORDERS AND INTRAUTERINE GROWTH RETARDATION

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stract Amniotic fluid lecithin has been measured in 92 mples from 75 patients with hypertensive disorders and normotensive pregnancies complicated by intrauterine owth retardation (IUGR) For the group with hyperten e disorders the lecithin concentrations were not gnificantly different from a reference material at any ge in gestation. Pre eclampsia associated with moder ly elevated blood pressure and complicated by IUGR owed significantly higher lecithin concentrations than y other diagnostic subgroup The lecithin concentra ns showed no relationship to maternal urinary estrogen retion. The value of serial estrogen measurements in edicting IUGR has been emphasized An evaluation of e amniotic fluid lecithin concentration in relation to re iratory function has been made Respiratory distress ndrome may occur even in growth retarded babies

INTRODUCTION

Hypertensive disorders in pregnancy with and without intrauterine growth retardation (IUGR) and normotensive IUGR carry a substantial risk of fetal death in utero due to placental insufficiency (8) These pregnancies are frequently terminated pre maturely with the added risk of respiratory distress syndrome (RDS) developing in the newborn There is a clinical impression that IUGR infants rarely develop RDS (27) Other recent reports suggest that such growth retardation as a result of placental insufficiency may in fact accelerate fetal pulmonary maturation (7 13 22) Furthermore maternal hypertension per se may have the same effect (13)

In view of the possibility of accelerated pulmonary maturation in such pregnancies it was of interest to investigate the relationship between sur t levels as measured by amniotic fluid leci thin concentrations maternal hypertension and cases of IUGR It was also of interest to study the relationship between the lecithin concentrations and the maternal urinary estrogen excretion $\approx(E_3)$ which is an accepted method of determining the function of the fetoplacental unit (4 13 21 23)

MATERIAL AND METHODS

Definitions

Hypertensive disorders

A Preeclampsia (48 patients) 1) Blood pressure (BP) at or above 140/90 mm Hg detected during the second half of pregnancy BP was measured at least twice with a minimum interval of 6 hours And in addition one of the following criteria 2) Proteinuria in a morning specimen of 1/4‰ (Esbach) or more 3) Generalized edema or weight gain of 2 kg/week or more

B Essential hypertension (3 patients) BP at or above 140/90 mm Hg recorded before and during pregnancy

C Pregnancy hypertension (16 patients) BP at or above 140/90 mm Hg appearing at any time during pregnancy without other significant signs and symptoms of pre eclampsia

In the test B and C are considered together and termed pregnancy hypertension

The lecithin concentrations were correlated to the de gree of maternal hypertension in the following manner

Moderate hypertension (52 patients) BP≥140/90 mm Hg and <160/110 mm Hg

Severe hypertension (15 patients) BP≥160/110 mm Hg

Intrauterine growth retardation (25 patients)

Birth weight at or below the 3rd percentile according to the classification of Bjerkedal et al (3) 23 out of these 25 small for gestational age infants were considered dysma ture

80 samples of amniotic fluid from 67 patients with hypertensive disorders and 12 samples from 8 patients with non-hypertensive IUGR were collected by transab dominal amniocentesis or at the time of Caesarian section The 80 samples from the group with hypertensive dis orders have been compared statistically at weekly inter

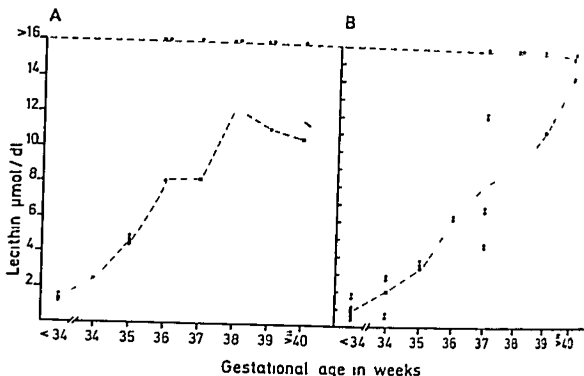


Fig 1 (A) Amniotic fluid lecithin concentration in 80 samples from patients with hypertensive disorders and (B) in 83 samples from the reference material related to gestational age × × Median values for both groups

vals using the Wilcoxon two-sided two-sample test with a reference material obtained during the last 8 weeks of pregnancy These samples were from normal pregnancies or from pregnancies where abnormalities were considered insignificant for fetal pulmonary maturation The same material was used in a previous report (24) Gestational age has in the text been given in completed weeks i e 39 weeks=273–279 days

Amniotic fluid lecithin was correlated to the various tic subgroups and to E_3 For this purpose the leci concentrations were divided into three groups

Low lecithin (11 patients) Concentrations at or below half of the median value of the reference material

High lecithin (11 patients) Concentrations twice the median value of the reference material or more

Appropriate lecithin (53 patients) The remaining samples

Comparison with the median value of the reference material was made at the corresponding week in gestation for each sample

E_3/24 hours was measured in 70 pregnancies by the method described by Brown et al (5) Concentrations based upon a material of normal pregnancies (4) were classified as follows

Normal E_3 Concentrations above −1 standard deviation (S D)

Subnormal E_3 Concentrations between 1 and −2 S D

Low E_3 Fall or not satisfactory rise in concentrations with one or more recordings below −2 S D

In the majority of patients evaluation of E_3 was based upon more than two measurements Evaluation of only one measurement was not attempted Assessment of all estrogen concentrations was made at the appropriate stage in gestation

Lecithin has been measured quantitatively in centrifuged amniotic fluid as previously reported (18, 2 Unit of substance has been given in micromoles per 100 ml of amniotic fluid µmol/dl Assessment of respiratory function the diagnosis of RDS and transitory RDS re ing supplemental oxygen for less than 4 hours has been as previously defined (18)

All cases with uncertain menstrual histories have been excluded This also applied to cases where an a discrepancy existed between the expected date of de ery calculated from the menstrual history and the ma ity of the newborn recorded by an independent pae trician

RESULTS

The lecithin concentrations for 80 samples from patients with hypertensive disorders are given in Fig 1A and the results of 83 samples from the reference material are given in Fig. 1B There is an obvious increase in the median values for both groups with time but also a very wide range Statistical analysis of the results at the same week of gestation for both groups gave no significant differences at any stage

The correlation between the lecithin concentrations divided into high appropriate and low le

Table I Relationship between the lecithin concentrations classified as high appropriate and low for gestational age respiratory distress and the various diagnostic groups of hypertensive disorders and intrauterine growth retardation

	No of patients	High lec	Approp lec	Low lec	RDS
Preecl. without IUGR	35	2	26	7	3
Preecl. with IUGR	13	6	7	0	0
Pregnancy hypertension without IUGR	15	1	13	1	0
Pregnancy hypertension with IUGR	4	1	1	2	3
Nonhypertensive IUGR	8	1	6	1	0
Severe hypertension	15	1	11	3	4
Moderate hypertension	52	9	36	7	2

gestational age and the diagnostic subgroups is summarized in Table I For preeclampsia with and without IUGR there is a difference in the distribution of the lecithin concentrations There were 13 infants with IUGR in this category and all had either high or appropriate lecithin concentrations This difference for preeclampsia is $\chi^2 = 12.48$ with a probability of significance $P = 0.002$ Pregnancy hypertension with and without IUGR as well as non-hypertensive IUGR had distributions of lecithin concentrations which showed no clear deviations from normal However the number of patients was small in two of these groups

Among those with hypertensive disorders 9 of 10 with high lecithin concentrations were found in pregnancies with moderate hypertension There were none with severe hypertension among the IUGR infants who had high lecithin concentrations

Six infants developed RDS and four were from pregnancies with severe hypertension Three of the infants had IUGR In the 75 pregnancies there were the intrauterine death 74 liveborn babies and no neonatal deaths

The relationship between E_3 in 70 pregnancies and the distribution of lecithin concentrations is given in Table II Both high and low lecithin concentrations were more frequently seen in the group with low E_3 than in those with normal or subnormal E_3 25 pregnancies with low E_3 resulted in the delivery of 17 IUGR infants (68%) Four of the 6 babies with RDS occurred in the low E_3 category and three of these were from pregnancies with severe hypertension There were 6 cases of high lecithin in the low E_3 group and none occurred in pregnancies with severe hypertension

Fifty samples of amniotic fluid were obtained from 50 patients within one week of delivery These pre-delivery lecithin concentrations together with serial measurements in three pregnancies with IUGR are shown in Fig 2 Lecithin concentrations >4 6 μmol/dl have previously not been associated with RDS except in maternal diabetes mellitus (24) Six babies of 12 with pre-delivery lecithin concentrations <4 8 μmol/dl developed RDS In two of these the distress was transitory only and of a more severe kind in the remaining four There were no signs of RDS in the other 6 infants with lecithin concentrations <4 8 μmol/dl or in the 38 with concentrations >4 8 μmol/dl The same was the case with the 24 infants not included in Fig 2

The three IUGR infants with serial lecithin measurements had low concentrations in repeated samples during the last 4 weeks of pregnancy Delivery was postponed after each measurement until the

Table II Relationship between the maternal estrogen excretion and the lecithin concentrations classified as high appropriate and low for gestational age intrauterine growth retardation and respiratory distress

	No of patients	High lec	Approp lec	Low lec	IUGR	RDS
Normal E_3	8	2	23	3	2	1
Subnormal E_3	17	1	13	3	6	1
Low E_3	25	6	14	5	17	4

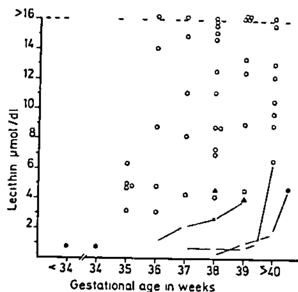


Fig 2 Amniotic fluid lecithin concentrations in 50 samples obtained within one week of delivery related to gestational age ×—× Serial lecithin analysis in pregnancies with growth retarded infants O no respiratory distress ● respiratory distress ▲ transitory respiratory distress

risk of RDS developing was considered reasonably small and the distress which occurred in two babies was not of a severe nature The three very early deliveries were in pregnancies with ominous rise in blood pressure and with fulminant eclampsia in one patient These three infants all developed RDS One of them had IUGR

The data of the calculated lecithin/sphingomyelin are not included since no additional information could be obtained from the material studied in this report

DISCUSSION

The lecithin concentrations in pregnancies complicated by hypertensive disorders in this study show a wide scatter with some concentrations quite high around 35–36 weeks of gestation and some fairly low close to term This picture has become familiar and the present material has been shown not to be statistically different from the reference group of similar size There is therefore no indication that maternal hypertension as such is capable of accelerating fetal pulmonary maturation as measured by amniotic fluid surfactant (12)

There is however widespread clinical agreement that RDS is not a feature of IUGR (7 22) Usher (27) even claims that he has yet to see infant with fetal malnutrition develop respiratory distress syndrome The association of good lung function in dysmature babies has been linked to the existence of a stressed situation before birth which has been thought capable of accelerating augmenting lecithin synthesis In the present study the finding of a highly significant relationship between mature lecithin concentrations in preeclamptic patients who gave birth to babies with IUGR is in agreement with this view Among the 13 infants in this category there were none with low lecithin concentrations for gestational age or respiratory difficulties For this group therefore sufficient stress may have existed to augment lecithin synthesis through endogenous steroid production. A comparison may be made with the situation whereby corticosteroid administration to the mother or the fetus seems to accelerate fetal pulmonary maturation (9 15 16 17)

The other infants with IUGR in this study had lecithin concentrations not different from the reference material No evidence of accelerated pulmonary maturation was therefore found in these groups Pulmonary maturation was even retarded in some cases Since small for gestational age infants comprise a heterogenous group it is possible that the cause of the growth retardation in the preeclamptic pregnancies was more clearly established and that the moderate hypertension associated with it was more capable of augmenting lecithin synthesis than either growth retardation associated with severe maternal hypertension or normal blood pressure Whatever the cause IUGR infants may certainly develop RDS As shown in Fig 2 serial amniocentesis was made in three patients who all delivered IUGR babies The fact that several samples in each patient had low lecithin concentrations clearly points out that pulmonary maturation may be delayed in some of these infants Indeed two of these three plus one more IUGR infant delivered before 34 weeks did develop RDS There are scattered reports of such infants developing RDS (1 14 22) It would in fact be surprising if a heterogeneous clinical entity as IUGR invariably should be blessed with a favourable outcome in this respect

Attempts were made to establish a relation between high and low lecithin concentrations with the maternal estrogen excretion As shown in Table II, no clear relationship existed This is in agreement with the findings of Freeman et al (11) Both high and

low lecithin concentrations were more frequently seen in the low E_3 group than in those with normal or subnormal E_3. Of the 6 infants with high leci[illegible] all were growth retarded and 5 were in the group of preeclampsia with moderate hypertension. Of the 5 infants with low lecithin/low E_3 none [illegible] the triad of IUGR and maternal preeclampsia with moderate hypertension. This appears to [illegible] the impression that such a situation may [illegible] surfactant production. On its own E_3 does not seem to bear any direct relationship to the am[illegible] lecithin level and its value was confined [illegible] ility to predict fetal growth or the lack of [illegible] and together with the lecithin concentrations [illegible] helped determine the optimal time of delivery.

In previous reports (19 25) lecithin concentrations >4.6 μmol/dl with the frequent exception of maternal diabetes have not been associated with RDS. In this series of experiments 50 patients had amniocentesis within one week of delivery. 38 had lecithin concentrations >4.8 μmol/dl with no signs of RDS and 6 babies with RDS all had concentrations <4.8 μmol/dl confirming our previous experience. Amniotic fluid lecithin therefore accurately seems to reflect both the state of maturity of the fetal lungs and the amount of surfactant reserve present. With low reserve stable alveoli are in addition dependant upon undisrupted surfactant synthesis during the final stages of pregnancy and after delivery. The mechanism of surfactant synthesis may be damaged by intrapartum complications (6 [illegible] 12 24 26). The combination of severe maternal hypertension/low E_3 in the presence of low lecithin concentrations was found in three of the 6 cases of RDS studied in this report. It is likely therefore that such complications are capable of producing RDS with greater frequency the lower the amniotic fluid lecithin concentration or surfactant reserve is. This likelihood is however considered small with lecithin concentrations >4.6 μmol/dl.

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CERVICAL CANCER IN WOMEN BELONGING TO A CYTOLOGICALLY SCREENED POPULATION

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tract Women belonging to the cytologically screened ulation of Stockholm in 1968 to 1974 and developing cal cancer of stage I to IV were studied The purpose to find out the number of women in whom the cancer preclinical stage was not detected at routine screen and the reasons for this fact It was found that 34 out women had never been cytologically screened The ining 143 women had been checked at mass screening r at private specialists or hospitals In 51 screened en the cancer was not detected until the women selves attended a doctor because of symptoms Thus women or 48% of the series the cancer escaped tion at an asymptomatic stage Errors causing a de r interruption of the follow up of patients with cious smears or colposcopic atypia were observed in ses Sixty four patients or 45% of all screened n had had at least one negative smear within 4 5 prior to discovery of the malignancy Out of these tients had got a negative smear within 3 years What might be the true evaluation of these negative s their influence on the continued management of omen was important In view of the results of this the 4 years interval of rescreening practiced in kholm seems to be too long Moreover the statement upported that the value of health screenings is teracted by the fact that the people most at risk are least likely to attend

INTRODUCTION

t value of population health screenings probably e the rate of the total female population in are the least likely to attend In a Norwegian dy the incidence of invasive cervical cancer ong never screened women was estimated to be e the rate of the total female population in ded (11) In Sweden cytological health screen has been practiced since 1958 and from 1968 ere has been a mass cytological screening pro- amme going on in Stockholm with the aim of screening the women every 4th year

The load on the gynecological clinics and cytolog ical laboratories continuously increases because of frequent checks up of a growing number of women with suspicious smears The risk of failure in the management of these cases might be considerable So for instance the presence of a high amount of false negative smears has been reported (3 4 11)

This study was undertaken in order to find out the frequency of cervical cancer or its preclinical stage escaping detection at routine screening and the reasons for this The women invited to the cytological population screening of the city of Stockholm and developing cervical cancer of stages I to IV were studied

Firstly the number of non attendance was esti mated Secondly the frequency and type of factors in the screening routine causing a delay or mistaken diagnosis were analysed The aim was finally to judge whether a screening interval of 4 years might be reasonable

MATERIAL AND METHODS

The material consists of those women invited to the cytological mass screening of the city of Stockholm in the years 1968 to 1974 in whom cervical cancer of stages I to IV was detected in this period During these 7 years a total of about 230 000 women born in 1920 to 1939 and in 1914 to 1915 were invited to the population screening at least once In 1968 the first year of screening women born in 1930 to 1934 were asked to attend That year cervical cancer was detected in 6 of these women From next year on women born in 1935 to 1939 who got cervical cancer were included in the series since they belonged to the population which had been screened In 1970 patients with cervical cancer born in 1925 to 1929 were added and so on (Table I)

Patients were looked for in the registry of the radio- therapy clinic Radiumhemmet and as a cross check

Table I *The number of those women belonging to the population of cytological screening in whom cervical cancer was observed and the years of diagnosis*

Year of diagnosis	Year of birth						Sum
	1930–34	1935–39	1925–29	1914–15	1920–21	19.2– 4	
1968	6						6
1969	11	5					16
1970	13	1	11	12			37
1971	5	1	9	11	7		33
1972	5	4	4	5	3	14	35
1973	5	5	7	4	2	8	31
1974	7	5	1		2	4	19
Sum	52	21	32	32	14	.6	177

in the registry of cancer at the Swedish Board of Health and Welfare Information about patients registered in 1968 to 1971 is recorded on a computer system Since information about patients in the subsequent years has not yet been fed into the computer system these women were searched for manually at the Registry of Cancer In this way the case records of 182 patients were collected and studied The addresses of the patients at the year of invitation were checked either by asking the patients themselves or at the church registries It was noticed that 5 women moved into the city the same year as they were to be asked to attend the screening Due to a delay in the information of registration of new inhabitants these women did not receive an invitation to the mass screening They were thus excluded The remaining 177 women were looked for in the registry of the cytological population screening. Information of patients not present in this registry was obtained either from the case stories and/or from the women themselves Finally private gynecologists contributed with information concerning earlier cytological checks

Control of the material

When comparing the names of patients of the registry of e Radiumhemmet with those of the computer lists it was observed that 18 patients (0%) were missing on the latter On the other hand 13 patients with dysplasia cancer in situ were wrongly present on the computer In the registry of the Radiumhemmet data on 6 at concerning either addresses or the year of birth was to be incorrectly recorded and the women were primarily excluded However the true conditions later confirmed on the computer lists

Table II *Distribution of microinvasive and invasive cervical cancer*

	Stage of cervical cancer		
	I A	I B–IV	Sum
Number of patients attending the mass screening	25	73	98
Number of patients screened elsewhere	8	37	45
Number of patients never cytologically examined	3	31	34
Sum	36	141	177

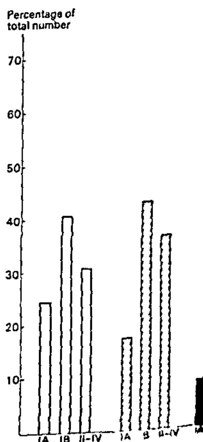


Fig 1 The percen stage of women checked elsew



[?] The stage of cervical cancer observed when the ...en consulted a physician because of symptoms ▨ ...nts cytologically checked ■ patients never cytolog... checked

RESULTS

...ng the years 1968 to 1974 cervical cancer of ...s IA to IV was detected in 177 women being ...ed to the cytological population screening of ...ity of Stockholm (Table I)

...dance

...ty-eight of these women did attend the screen... Among the rest 45 patients had had one or ... smears at a private specialist at hospitals or ...where In fact 141 women had been cytologi... examined at least once within 6 years and two ...ed within 8 years prior to the detection of the ...er The remaining 34 patients had probably not ...ny smear taken previously In 4 cases it cannot ...olved since information is lacking in the case ...s and the women are dead (Table II)

Distribution of the cancer related to stage and the way of its detection

Fig 1 shows the percentage distribution of cervical cancer related to stage at the time of detection of patients attending the mass screening of women checked somewhere else and of women never cytologically examined There is no distinct difference in distribution of stage of cancer between women attending the mass screening and women checked elsewhere However the high percentage of cancer of stage II or more in women who had never been screened is noteworthy This is also prominent in Fig 2 showing the percentage distribution of cervical cancer by stage in those screened (mass screening *and* elsewhere) and unscreened women that consulted a doctor because of symptoms Out of 87 women with atypia in the smears 47 were sent to Radiumhemmet within ½ year s time In 51 screened women the malignancy was not detected until symptoms made the patients visit a doctor Thirty four of these had attended the mass screening (Table III)

Failures

Two patients only neglected a follow up being recommended because of a suspicious smear Physicians mistakes were observed in 23 cases In 6 of these the follow up was interrupted since the women got a negative smear after one or more positive ones In three cases there was an atypical colposcopic appearance but since the smear was negative no check up was carried through For unknown reasons there was no check up in the remaining 14 women in spite of atypia In 14 patients the malignancy was not detected until symptoms made the women visit a doctor The remaining women went for another routine check later (Table III)

Negative smears

Smears judged as belonging to Pap II are not referred to as negative in this study Women with negative smears earlier than 4 5 years before the cancer was detected are not included

Out of 98 women attending the mass screening 30 had got a negative smear within 4 5 years prior to detection of the cancer and out of 84 women checked either both at mass screening and elsewhere or only somewhere else 39 got a negative smear at the check elsewhere (Table IV) Five of these women had had a negative smear both at the mass screening and at the check elsewhere On

Table III *The way of detection of the cervical cancer in 143 cytologically screened patients*

Patients with	The cancer was detected				
	During follow up because of suspicious smear			At a later routine check initiated by the patient	When the [illegible] attended a doctor because of symptoms
	Within ½ year	½–2 years	>2 years		
Suspicious smears	47	8	7		3
Suspicious smears lost by mistake				7	7
Suspicious smears or colposcopic views and negative smears lost by mistake				4	7
Negative smears				19	34
Total	62			30	51

patient got a negative smear both at the first and second control at mass screening In one woman only the cancer was discovered at the second con trol at mass screening about 4 years after the first one

By adding the women neglecting the mass screen ing but checked elsewhere to those attending the mass screening it was found that 64 patients or 45% of the screened women had had a negative smear within 4 5 years prior to detection of the malignancy (Table IV) This number includes 7 women with a negative smear at private checks in whom atypia was later observed at the mass screening and 4 patients with a negative smear at the mass screen ing in whom atypia or cancer was later detected by private specialists Five women with one or more negative smears after conisation due to can cer in situ performed 1 to 7 years earlier later developed invasive cervical cancer Table [illegible] the time interval between the last [illegible] and the date of detection of the cancer [illegible] stage In 83% of the women the [illegible] detected within 3 years

Later on 23 of the patients with [illegible] went to another routine check at [illegible] malignancy was observed The remaining [illegible] en did not seek medical advice until [illegible] gave rise to symptoms (Table III)

DISCUSSION

Attendance and stage of cancer detec ed

Forty percent of the women invited to [illegible] screening of Stockholm failed to appear [illegible] the same figure was observed in this [illegible] 45% of the women developing cervical [illegible]

Table IV *The way of cytological control and the amount of patients with a negative smear [illegible] prior to detection of cervical cancer*

Smears taken	Total number of patients	Number of patients with negative smears [illegible] 4 5 years prior to the diagnosis of cancer		
		At mass screening	Both at mass screening and elsewhere	Elsewhere
At mass screening only	59	14		
Somewhere else	45			3
At mass screening *and* some where else	39	11	5	11
Percentage of patients with negative smears	64	25+5		34 5
Number of patients with negative smears	45%	31%		44

Table V The time interval between the last negative smear and the date of discovery of the cervical cancer related to stage

Stage of the cancer	Time in years			
	0 5–1	≤2	≤3	≤4 5
IA	2	3	2	
IB	5	12	9	7
II–IV	6	8	6	4
Sum	13	23	17	11

non-attendants of the mass screening The finding that a good half of these women were regularly checked somewhere else is in accordance with earlier observations (2 5 11) However the proportion of true non attendants among women of Stockholm getting cervical cancer (19%) is quite high compared to the one observed in total population invited to cytological health screenings (<6%) (8) This result supports the proposal that the women most at risk are the least likely to attend health screenings

Patients with *micro-invasive and occult cervical cancer* are included since they were treated at the radiotherapy clinic The majority of the cancer of stage I A was diagnosed at mass screening and at routine checks elsewhere It was seen in 3 patients only of those never checked (Table I Fig 1) The cancer of the unscreened women generally had progressed to a more serious stage than that of those screened women in whom the cancer was *detected when they attended a doctor* because of symptoms This discrepancy also noted by Pedersen in Norway (11) accentuates the seriousness of non appearance and/or indifference of the never screened women

Failures

The significance of dysplasia and cancer in situ as a precursor of invasive cancer is not fully clear and has even been *doubted (7) The main questions deal* with the length of the preinvasive stage and the proportion going to invasion A follow up of patients with dysplasia or cancer in situ without any biopsy or treatment is hard to perform for ethical reasons In the 25 women of this study on whom follow up was incorrectly interrupted such an outcome was realized However as long as we do not know the percentage of suspicious smears never developing into invasive cancer the problem can not be solved

In two counties of San Diego the cases of invasive cervical cancer diagnosed in 1967 were studied and preventable factors recorded by Martin (9) His purpose was to estimate the efficiency of a 10-year screening project It was observed that in all but 3 out of 76 cases there were probable errors Considering the result of the present study that in 36% of cytologically checked women the malignancy was permitted to progress until it gave rise to symptoms Martin s statement of a low level of efficiency of screening activity might be true

A reason for the low efficiency of screening activity might be the heavy load of gynecological clinics *with a continuous increase of patients repeatedly* checked due to suspicious smears It might happen that the doctor classifies a suspicious smear preceding a normal one as due to coincidence or inflammatory changes and interrupts the follow up Since 8 women developing invasive cancer were lost in this way it is reasonable to expect a higher number of cancer in situ escaping detection out of similar reasons

The negative smear

The presence of a rapidly appearing type of cervical cancer according to the theory of Ashley would lower the effectiveness of screening (1) Such a cancer might have been more frequent among the 64 women with previous negative smears compared to the remaining screened women However some *workers observing patients with negative smears* preceding an invasive cervical cancer discussed the possibility of laboratory and sampling failures (2 3 6 9 11) Whatever might be the correct evaluation of the negative smears of this study a screening interval of 4 years seems to be too long

Some authors point to the fact that the incidence of dysplasia and cervical cancer progressively decreases during repeated re screenings instead of *remaining constant as expected (4 13) Coppleson* et al proposed that this is due to the entry of a continuously decreasing number of cases previously falsely recorded as negative In the present series about half of the smears proved to be incorrectly evaluated (12) Recently a proposal was made to take two smears at a time to diminish the risk of sampling failure and error of evaluation of the material (14) In fact 86% of improvement of

detection of abnormal cytology was reached in this way

In conclusion it can be stated that with a higher efficiency of screening activity the 51 women not detected might have been caught earlier and saved from highly malignant disease (Table III)

ACKNOWLEDGEMENT

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ASSESSMENT OF ANTERIOR PITUITARY FUNCTION DURING THE POST PARTUM PERIOD

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From the Departments of Obstetrics and Gynaecology (Head Prof P Jarvinen) and Physiology (Head L Hirvonen) University of Oulu Oulu Finland

ract In order to assess anterior pituitary function ng the puerperium 0 women were studied by 14 venous LRH and 10 TRH stimulation tests within 0 days post partum The basal FSH level (150–340 ml) was within the normal non pregnant range for the cular phase of the menstrual cycle (50–350 ng/ml) and not increase after 100 μg of synthetic LRH The TSH 8 μU/ml) was high and increased after 200 μg of hetic TRH about twofold Obstetrical parameters milk excretion pregnancy complication type of de ry or the amount of bleeding during delivery) were not ciated with significant changes in FSH or TSH levels the responses to TRH stimulation

hough anterior pituitary function during men ual cycles has been evaluated repeatedly the erperal period apart from extensive physiologi changes has received little attention The st partum period is a sensitive one for a woman example it has been estimated that 4 per cent of women who lose more than 800 ml of blood dur labour suffer some transient ischaemic injury to anterior pituitary although post partum pan opituitarism (Sheehan s syndrome) is rare (8) The present study was performed in order to aluate anterior pituitary responsiveness to lute ing hormone releasing hormone (LRH) and thy rophin releasing hormone (TRH) in puerperal omen with special reference to various types of gnancy and delivery

MATERIAL AND METHODS

enty women volunteered for this study Clinical data shown in Table I For 10 of them a separate LRH ulation test, for 6 cases a separate TRH test and for 4 es a combined LRH and TRH test were performed 2–10 days post partum

The stimulation test was started at 07 30 after an over night fast The patients were in supine position during the test and a venous cannula was used Three basal samples were taken 30 min 15 min and immediately before the intravenous injection of 100 μg synthetic LRH and/or 200 μg synthetic TRH (Ferring AB Sweden) in 5 ml sterile water Blood samples were taken 5 10 15 20 30 40 60 90 and 120 min later Serum was separated and stored at −18 C until assayed

Serum follicle stimulating hormone (FSH) luteinizing hormone (LH) and thyrotrophin (TSH) were determined from a sample volume of 200 μl by a double antibody radioimmunoassay

Purified hormones and antisera were kindly furnished through the courtesy of the NIAMDD The hormones were labelled with 125 I (IMS 30 Amersham) at specific activities ranging from 100 to 200 mCi/mg The antisera were used in dilutions recommended by NIAMDD In the semilog plot the inhibition curve was linear between 10 and 500 ng of FSH (LER 907) per tube 5 and 100 ng of LH (LER 907) per tube and 0 2 and 50 μU of TSH (MRC 63/89) per tube The immuno-complex was precipitated by sheep antirabbit serum Normal rabbit serum and 0 01 molar EDTA (final concentration) were added to obtain complete precipitation After 24 hrs the precipitates were separated by centrifugation All the determinations were done in duplicate The intra assay coefficient of variation varied from 7 to 12% and the interassay coefficient of variation from 10 to 15%

RESULTS

Before the injection of LRH the individual FSH values varied from 155 to 340 ng/ml and after the administration of LRH from 141 to 345 ng/ml LRH stimulation did not increase the level of FSH in any patient in the series (Table II) The unresponsive ness of the anterior pituitary remained the same if the LRH test was performed alone or combined with the TRH test Various obstetrical parameters were not associated with significant differences in

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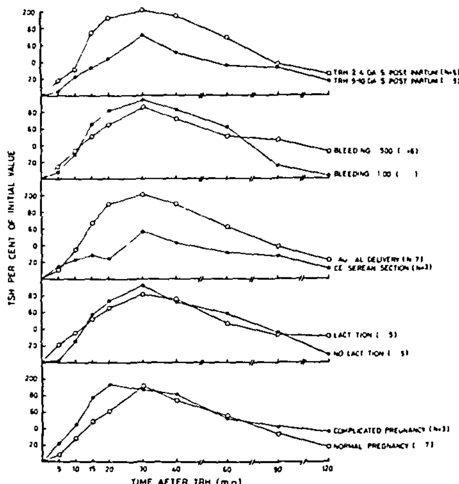
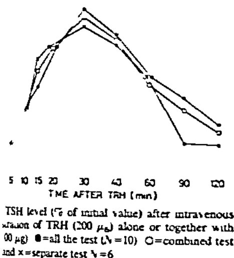


Fig 1 TSH level (% of ini-tial value) after [illegible] administration of TRH [illegible] µg) in various groups of patients

Table I *Volunteers investigated with intravenous LRH and/or TRH stimulation tests during post-[illegible] period*

Volun	Age	Parity	Type of pregnancy	Delivery: Pregnancy week	Delivery: Type	Delivery: Bleeding (ml)	Milk excretion	Test	[illegible]
1	22	1	Normal	39	Vaginal	<500	+	LRH	3
2	24	1	Normal	39	Vaginal	<500	+	LRH	5
3	[illegible]7	[illegible]	Pre-ecl	38	Vaginal	<500	−	LRH	3
4	35	[illegible]	Rh imm	33	Section	1 [illegible]00	−	LRH	6
5	34	[illegible]	Normal	39	Section	700	+	LRH	5
6	[illegible]0	1	Normal	40	Vaginal	1 000	−	LRH	4
7	[illegible]0	1	Normal	41	Vaginal	<500	+	LRH	4
8	25	1	Normal	40	Vaginal	1 100	+	LRH	[illegible]
9	30	6	Rh imm	37	Section	1 700	+	LRH	[illegible]
10	[illegible]4	1	Pre-ecl	37	Vaginal	[illegible]00	−	LRH	[illegible]
11	[illegible]5	1	Normal	40	Vaginal	1 100	+	TRH	[illegible]
12	18	1	Normal	40	Section	<500	−	TRH	[illegible]
13	19	1	Normal	38	Vaginal	1 [illegible]00	−	TRH	[illegible]
14	30	6	Rh imm	37	Section	1 700	+	TRH	[illegible]
15	30	[illegible]	Normal	38	Vaginal	1 [illegible]00	−	TRH	10
16	24	1	Pre-ecl	37	Vaginal	<500	−	TRH	[illegible]
17	[illegible]4	2	Pre-ecl	39	Vaginal	<500	+	Combined	[illegible]
18	36	1	Normal	39	Section	<500	+	Combined	[illegible]
19	4[illegible]	5	Normal	38	Vaginal	<500	−	Combined	[illegible]
20	30	3	Normal	39	Vaginal	<500	+	Combined	[illegible]



TSH level (% of initial value) after intravenous stration of TRH (200 μg) alone or together with 00 μg) ● = all the test (N = 10) O = combined test and x = separate test N = 6

al FSH levels although they were somewhat d in patients following caesarean section irtum haemorrhage and in patients with in nt or no milk secretion

obtained "LH values were high ranging 0 to 1430 ng/ml with no response to LRH tration This was mainly due to human ic gonadotrophin (HCG) as verified with ation studies (see discussion)

basal level of TSH varied within 3 3 to 8 8 The absolute TSH values as the means and after TRH stimulation are shown in II Every volunteer responded to TRH ion, the greatest increase in TSH level be % and the smallest 148% The relative veness of the pituitary to TRH was not t related to obstetrical parameters al the response was slightly depressed in pa ter caesarean section (Fig 1) The pituitary to TRH was similar if TRH was ad ed alone or combined with LRH (Fig 2) de-effects were observed after the admini stration of LRH After TRH sweating was complained of by one woman and flushing by 7 women. After combined LRH TRH tests no cumulative harmful side-effects were observed. TRH did not improve the milk secretion in any woman

DISCUSSION

In every puerperal woman the pituitary gonadotrophin FSH could be detected and the range of 155–540 ng ml fell in our normal non-pregnant level during the follicular phase of the menstrual cycle of 50–350 ng ml This finding is in accordance with previous results (4) but conflicts with low or undetectable FSH levels in the puerperium reported by some investigators (2 1.) In our volunteers LRH did not stimulate the FSH secretion 2–10 days post partum Previously Canales et al (1) observed the same pituitary unresponsiveness to intravenous administration of 50 μg of synthetic LRH within the first 48 hrs post partum but some response 15 days after delivery LeMaire et al (10) could show some response in LH level after a subcutaneous injection of 100 μg of LRH in 3 puerperal women 6 weeks post partum but no response 3 weeks after delivery It remains to be elucidated how long the pituitary tolerance to LRH lasts in puerperal women and what is its cause

The TSH level during post partum time was high as found by the others (6 11) The pituitary reaction to TRH in puerperium is maintained Kannan et al (9) also found about twofold increase in TSH level after 250 μg of synthetic TRH in 3 subjects tested one week post partum Somewhat greater responses to TRH have been reported in 3 post partum women studied by Gautvik et al (5)

No obstetrical parameter studied in our investigation was shown to have any influence on the FSH or TSH level or the responses to TRH stimulation Lactation has been observed to be associated with

Mean FSH (LER 907) and TSH (MRC 63/89) levels before and after LRH or TRH stimulation

	−30	−15	0	5	10	15	70	30	40	60	90	1.0 min
)												
	217 46	217 40	200 43	193 30	214 54	212 42	206 34	206 42	224 58	716 49	208 41	200 4.
ml)												
	5 3 1 1	5 4 1 6	5 0 1 1	5 9 1 5	6 9 1 6	8 2 2 3	8 9 3 1	9 9 2 4	9 2 7 3	8 1 2 1	7 1 2 0	6 4 1 8

Table I *The incidence of Chlamydiae Mycoplasmas and bacteria in the cervix and the Fallopian tubes (n=21)*

	Cervix	Tubae
Chlamydiae	6	1
Mycoplasma hominis	9	0
T mycoplasma	14	1
Neisseria gonorrhoeae	7	1
Other bacterial pathogens	17	2

the Fallopian tubes as well One patient with minor symptoms for two weeks before the acute incident had high unchanged CF titres (1/128–1/256) although no organism could be isolated In these five patients no other pathogenic microorganism was isolated from the tubal exudate

DISCUSSION

Previous investigators using a laparoscopic technique for the collection of specimens (5) have reported acute salpingitis associated with Mycoplasma hominis T mycoplasma Neisseria gonorrhoeae and some other bacterial pathogens Our study is too small to allow any comments on a quantitative basis but the findings are in accordance with earlier reports Some studies claim that Chlamydia only gives rise to silent infection in the lower genital tract and only with minor symptoms (3 8) Hilton et al (3) mention a case with prolonged pelvic infection where Chlamydia was isolated from the cervix In epithelial infections urethritis and cervicitis the CF test is relatively insensitive as a diagnostic tool A significant increase in CF antibody titres or an unchanged high titre is therefore suggestive of a deep-seated infection with a massive immunogenic stimulation by the causative agent The finding of Chlamydia in cervical secretions in 6 out of 21 patients is in accordance with earler s[illegible] serological evidence of continu[illegible] Ch[illegible] fection in five patients with a[illegible] gether with the occurrence of Chlam[illegible] lopian tubes in one of the five may [illegible] C[illegible] mydia subgroup A is a causative [illegible] salpingitis

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LETTER TO THE EDITOR

t interest I have read the paper entitled
ent of imminent premature labour by O
M Gummerus and S Saarikoski Acta
Gynecol Scand 54 95 1975 and hope you
me some comments The trial is labelled a
controlled trial but it does not fulfill
ria for such a trial The four modalities of
were carried out in four different depart
n two separate hospitals and the observa
hus made by four different staffs on one
y each It is stated that every other patient
at the University Hospital fulfilling the
was sent to Dept I and every other to
I seriously doubt that the decision to
to send the patients was made
criteria for admission to the study had
1 The same objection applies to the
School Hospital
was started immediately on admis
there was no attempt made to determine
the patients were in true progressive lab-
in false labour The excellent results ob
placebo indicate that a very high per
must have been in false labour if not we
use dextrose/water and forget about drugs
1
nfusion rate of alcohol is obviously mis
The infusion rate must have been ca 9 ml of
per minute and not 0 8 ml If this as
is correct the dosage is similar to the one
by Fuchs et al (1967) but in our material
was often continued for more than 6
repeated if after initial arrest of labour
tions recurred
of ethanol to prevent premature birth is
but it is true that there is a paucity of
ons However they are not all as negative
quoted by the authors on the contrary
there was a controlled study as early as
ith very good results (3) I would hope that
lly designed studies than this one could
d out in the two institutions before the con
is reached that ethanol is useless in threat
ened premature labour In particular I wish the authors would address themselves to the difficult question of distinguishing false labour from progressive labour which is crucial for studies such as these

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Rejoinder

We thank the editor of Acta Obstetricia et Gynecologica Scandinavica for the possibility of letting us make our remarks immediately upon the comments made by Dr Fuchs on our article The kind of research presented in our article is difficult because it often takes a long time to get enough material Therefore the keeping in hands of the research also becomes difficult We had the possibility of gathering material from two different maternity hospitals which are the same size and managed along the same principles One member of the research group was working at the Women s Clinic in Helsinki and one at the Midwifery School Hospital In this manner the length of the study could be limited to one year

The selection of patients for the groups presented in the investigation was performed at random Each patient herself chose the hospital where she wanted to give birth The doctor working in the outpatients department of the hospital who did not

belong to the research group decided after having examined the patient whether she needed hospital care or not After this the nurse sent every first one of the patients to Department I and every second one to Department II

False labour cases are expected to exist in our material But we could not begin to choose our material by eliminating false labour cases after our deliberation We considered that if the groups were large enough an equal amount of false labour cases would exist in each group thus being of no significance when the groups were compared with one another

Dr Fuchs quite rightly takes an interest in our maybe a little unclear explanation of what exactly was the infusion rate in our research yet after a careful reading of the article it becomes clear it was 0 8 ml/min ethyl alcohol i e 8 3 ml/min mixture solution Thus the infusion rate was the same as in Dr Fuchs own experiments

When referring to earlier research we have listed only verified experiments This is why the publications mentioned by Dr Fuchs have not been cited

We have not stated in our article that the alcohol would be useless in threatened premature labour as Dr Fuchs claims We only said On the basis of the present study it is clear that alcohol [illegible] administered intravenously in fairly large doses not result in better therapeutic results than placebo

We think that the confidence in alcohol as agent inhibiting premature uterine [illegible] begun to vacillate among obstetricians We [illegible] point at e g the Gallup inquiry on the [illegible] and therapy of premature labour (1) Eight [illegible] American obstetricians expressed their [illegible] questions presented Five of them re[illegible] starting the therapy with β sympathomimetics [illegible] only two the starting of it with alcohol One of [illegible] latter kept β sympathomimetics as a second [illegible] drug

Clinical practice speaks in favour of our [illegible] Thank you Dr Fuchs for the comments

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ANNOUNCEMENTS

International Symposium has been organized on ulation The symposium will be held at C S Human Growth and Development Wayne University School of Medicine Detroit on April 1977 (following World Congress Fertil Steril h Fla.) Forty three national and international will discuss oogenesis folliculogenesis structure tructure and scanning electron microscopy of ovula endocrine neuroendocrine and neuromuscular of ovulation intrafollicular endocrine pro- ypes of anovulation physical biophysical and en techniques to predict and detect ovulation ovarian ultrasonics induction of ovulation by clomiphene gonadotropins or GnRH regularization of ovulation treatment of cycles with corpus luteum defects or polycys tic ovaries and cervical mucus sympto-thermal methods and lactational amenorrhea in relation to natural family planning A M A accreditation Deadline to submit abstracts of contributed research papers is November 1 1976 For abstract forms and additional information Dr E S E Hafez Reproduction Physiology Laboratories C S Mott Center for Human Growth and Development Wayne State University School of Medicine Detroit Michigan 48?01 (Tel 313/577 1011)

Acta Obstet Gynecol Scand 55 383–385 1976

CERULOPLASMIN AND COPPER LEVEL IN MATERNAL AND CORD BLOOD AND IN THE PLACENTA IN NORMAL PREGNANCY AND IN PRE ECLAMPSIA

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Mohyi A Ramadan and Mohamed B Sammour

From the Department of Biochemistry (Head Prof M A Ramadan) and the Depart ient of Obstetrics (Head Prof M B Sammour) Faculties of Medicine and Science Ain Shams University Cairo Egypt

act Copper and ceruloplasmin were assayed in ma and cord blood sera and in the placenta of 10 women ormal pregnancies in 10 patients mild and 10 with pre-eclampsia Copper and ceruloplasmin levels significantly elevated in the maternal blood of pre ptic patients as compared with normal pregnant n. The placental and cord blood concentrations of r and ceruloplasmin showed non significant s, which indicates that their increase in the mater od is not of placental origin

copper is distributed approximately equally n erythrocytes and plasma except in preg when the concentration rises in the plasma t 96% of the plasma Cu is firmly bound to an bulin as ceruloplasmin containing eight atoms r in each molecule (11) a variable but smal ount is less firmly bound to albumin and a mall quantity is dialysable An increased Cu t in the serum during pregnancy has been ed by serveral authors (3 12 5) Freedman et studied the serum Cu level in healthy women various months of pregnancy and in pregnant with various pathological conditions They ded that a progressive increase in the serum r level occurred during pregnancy followed ow decrease with return to normal levels only eeks after pregnancy O Reilly & Loncin (7) d a progressive increase in ceruloplasmin starting from the second trimester of preg and reaching a maximum level at the time ery followed by a drop 6 weeks postpartum also reported that blood from the neonate d a mean ceruloplasmin level below the lower limits of the normal range (4 6) Zarafonetis & Kales (15) reported that ceruloplasmin degraded serotonin at pH 7 4 O Reilly (7) suggested that the increasing serum ceruloplasmin during pregnancy could play a role in ensuring that the increasing blood serotonin levels did not lead to increased levels of free plasma serotonin Despite the in creased blood serotonin there was not a proportionate increase in 5 hydroxyindole acetic acid (5 HIAA) output in the urine because of the degra dation of the 5 hydroxyindole one of the metabolities of serotonin by ceruloplasmin

Ahlmark (1) and Swanberg (13) suggested that ceruloplasmin and histaminase serum levels may constitute a very sensitive indicator for the normal course of pregnancy and placental function

The purpose of this study was to investigate the level of copper and ceruloplasmin in normal preg nancy and in pre eclampsia in maternal sera in the placental extract and in cord blood and to study the significance of any variation

MATERIAL AND METHODS

Thirty pregnant women were selected from the maternity department of Ain Shams University hospitals so that 10 cases represented normal uncomplicated pregnancy as a control series 10 cases were of mild pre eclampsia and 10 cases were of severe pre-eclampsia This classification of pre-eclampsia was according to that previously described by Ramadan Sammour Khalil & Eisa (8)

Maternal blood samples were collected before the onset of labour whereas cord blood and placenta were taken immediately after delivery Deliery was in all cases per

m and in the placental extract were significantly reased in mild and severe pre eclamptic patients as compared with normal pregnant women The rase from mild to severe pre eclamptic patients not significant in the placental extract

) Cord blood ceruloplasmin was appreciably er than the levels of the maternal blood and reased non significantly from normal to pre mptic cases (Table II)

statistical analysis of all the data was carried using Student s *t* test and the equivalent lues were calculated to indicate the signifi e

DISCUSSION

work conducted by Zarafonetes (15) and by lly (7) in connection with the role of cerulo-in in oxidation of serotonin (5 HT) and its bolic product 5 hydroxy indole acetic acid AA) prompted us to study its concentration in lacenta and cord blood in relation to the ma l blood level This investigation is a continua of our previous work on serotonin in the ma l sera and the placenta (8)

delivery the copper level in the maternal increased significantly in severe pre ptic cases as compared with normal pregnant n but in mild pre eclapsia the increase was gnificant These findings agree with those of on (3) O Leary et al (5) and Freedman et al s increase in copper in maternal serum was flected either in the placental tissue or in the lood This indicates that the placenta is not urce of the increase in the maternal blood r It may be attributed to its release from tissues such as the liver The low level of r in placental tissue also affected its concen n in cord blood which showed a further de according to the severity of the toxemia concentration of ceruloplasmin was parallel t of copper where it showed a significant in in maternal serum a slight increase in the a and progressive decrease in cord blood in lampsia as compared with normal pregnant (Table II)

blood ceruloplasmin concentration in severe lampsia was more than double the level in l pregnant women at delivery and also signifi higher than in cases of mild pre eclampsia arked change in ceruloplasmin level in maternal blood with no significant change in placental and cord blood indicate that this rise is not of pla cental origin as mentioned with respect to copper concentration

The decreased activity of ceruloplasmin in cord blood corresponds to its copper content and con firms the results of O Reilly (6) and Markowitz et al (4)

The high concentration of ceruloplasmin in ma ternal sera of normal pregnancy and pre eclampsia at delivery should reduce the free unprotected sero-tonin in these sera yet it was found to be signifi cantly high (8) This can be explained by consider ing that ceruloplasmin is not the main oxidase of serotonin and its metabolic products Furthermore monoamine oxidase and its rise in pregnancy did not prevent the increased blood serotonin level from exerting its effects on the uterus and placenta The significance of the rise of ceruloplasmin in sera of pregnancy and toxemic patients still needs fur ther investigation The increase may be proportion al to the serotonin rise or there may be inhibiting factors in pregnancy toxemia preventing its func tion

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Table I *Copper concentration in ten normal pregnancies and twenty pre eclamptic patients [illegible] as μg/100 ml serum and μg/100 mg fresh placenta*

	Maternal blood			Cord blood			Placenta		
		Pre eclampsia			Pre-eclampsia			Pre eclampsia	
	Normal	Mild	Severe	Normal	Mild	Severe	Normal	Mild	Severe
No of cases	10	10	10	10	10	10	10	10	[illegible]
Range	170–[illegible]00	175–[illegible]05	195–250	95–115	95–1[illegible]0	90–115	8–1[illegible]	10–[illegible]	[illegible]
Mean	183 9	192	227 7	108 6	108 3	103 8	10 1	11 0	[illegible]
S D (±)	11 01	9 81	18 02	6 58	8 66	7 94	1 44	0 81	[illegible]
Test of significance (P)	N S (Normal vs Mild)			N S (Normal vs Mild)			N S (Normal vs Mild)		
	P<0 001 (Normal vs Severe)			N S (Normal vs Severe)			P<0 05 (Normal vs Severe)		
	<0 001 (Mild vs Severe)			N S (Mild vs Severe)			N S (Mild vs Severe)		

vagina with no difficult interference Anaesthesia when needed was by either local infiltration or pudendal block

The blood samples were left to clot and serum was then collected by centrifugation and kept at 4°C for enzyme assay within 24 hours Placental samples were obtained excised and washed according to Ramadan et al (8) homogenized in an equal volume of ice-cold water then centrifuged and the clear supernatent homogenate was adjusted to a known volume for estimation of both copper and ceruloplasmin by taking 3 ml of the homogenate for copper assay and 0 1 ml for ceruloplasmin assay The same amounts were taken from the serum for both copper and ceruloplasmin assay For every sample the assays were carried in duplicate according to the methods of Ventura & King (14) and Ravin (10) for determination of copper and ceruloplasmin respectively in serum and placenta The results for copper are expressed as μg/100 ml serum and μg/100 mg fresh placental tissue But for ceruloplasmin the results are given as mg/100 ml serum and mg/100 mg fresh placental tissue

RESULTS

(1) The concentration of copper in maternal s[illegible] showed a non-significant increase when com[illegible] normal pregnancy with mild pre eclampsia [illegible] increase in copper concentration was signific[illegible] severe pre eclampsia when compared with no[illegible] pregnant women and mild pre eclamptic cases

(2) The cord blood copper concentration [illegible] much lower than its corresponding level in the ma[illegible]ternal serum and it showed a non-significant [illegible] in mild and severe pre eclamptic cases

(3) The placental copper was remarkab[illegible] with slight change in mild and severe pre e[illegible] patients when compared with the normal [illegible] (Table I)

(4) Ceruloplasmin concentrations in [illegible]

Table II *Ceruloplasmin level in 10 normal pregnancies and twenty pre eclamptic patients [illegible] expressed in mg/100 ml serum and mg/100 mg fresh placental tissue)*

	Maternal blood			Cord blood			Placenta		
		Pre-eclampsia			Pre eclampsia			Pre eclampsia	
	Normal	Mild	Severe	Normal	Mild	Severe	Normal	Mild	Severe
No of cases	10	10	10	10	10	10	10	[illegible]	[illegible]
Range	21–43	49–65	68–[illegible]0	10–19	10–16	10–16	13–18	16–1[illegible]	[illegible]
Mean	3[illegible] 5	57 9	81 2	13 1	12 4	11 9	14 8	[illegible]	[illegible]
S D (±)	6.95	5 85	7 0[illegible]	7 88	2 0[illegible]	[illegible] 1	1 61	1 [illegible]	[illegible]
Test of significance (P)	P<0 001 (Normal vs Mild)			N S (Normal vs Mild)			P<0 0[illegible] (Normal vs Mild)		
	P<0 001 (Normal vs Severe)			N S (Normal vs Severe)			P [illegible] (Normal vs Severe)		
	P<0 001 (Mild vs Severe)			N S (Mild vs Severe)			N S (Mild vs Severe)		

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HISTAMINE METABOLISM AND FEMALE SEX HORMONES IN WOMEN

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Oral combined contraceptives did not seem to ... ine metabolism in females During treatment ... hormones in four amenorrhoeic pa... was a tendency towards increasing excretion ... histamine (MeHi) followed by a sudden decrease ... ponding to changes in the urinary estrogen The ... of methylimidazoleacetic acid (MeImAA) ... that of MeHi The findings support the ... that an endogenous surge of estrogen may ... tamine turnover in women Women of post ... age have about the same histamine metabo- ... younger menstruating women Estrogen medica ... symptoms of hot flushes or sweats but did ... the histamine turnover

INTRODUCTION

... metabolism seems to be influenced by ... normal menstrual cycle (11) The women in ... showed individual variations in the ex... of both histamine and its metabolites There ... significant difference in the excretion during ... and post ovulatory phase However the ... excretion of methylimidazoleacetic acid ... A) showed a tendency to increase at the ... of ovulation Also there seemed to be a ... correlation between the excretion of es... nd that of methylhistamine (MeHi) ... women Green et al (7) reported that ... might influence the urinary excretion of ... nd MeHi The cases however were few ... and the analyses were not performed ... ndardized dietary conditions ... present investigation represents an extension ... ous studies on the influence of female ... mones on histamine metabolism and in ... the effect of oral contraceptives ovulation stimulation with gonadotrophic hormones and estrogen substitution at postmenopausal age

MATERIAL AND METHODS

Sixteen healthy women were treated with different oral contraceptives over 17 tablet periods and a total of 77 urine samples were collected In 10 of these women urine were also collected during their normal menstrual cycle (39 samples) The excretion of histamine (Hi) and methyl histamine (MeHi) was measured

A second group comprised four women with secondary amenorrhoea Two of the subjects were studied during one period of stimulation with gonadotrophic hormones one was studied during two periods and the fourth during four periods of stimulation In this group the excretion of histamine and metabolites was studied as well as that of total estrogen and luteinizing hormone (LH) The progesterone level in plasma was measured to decide whether ovulation had taken place

A third group included 20 postmenopausal women Ten of them had subjective symptoms such as hot flushes and/or sweats The other ten had no subjective symptoms at all (Table I)

In this group of women urine collection was performed twice on two consecutive days and this was repeated approximately four weeks later Histamine and MeHi in the urine were determined At one of these days serum was taken for analysis of LH and follicle stimulating hormone (FSH) and estrogen excretion was determined in the urine The 10 women with symptoms were studied in the same way before and during treatment with estrogen (ethinylestradiol 20 μg per 24 hours) four weeks later

Urine was collected in 24-hour portions The urinary samples were immediately placed in a refrigerator at +4°C When samples for hormone analyses had been withdrawn the urine was mixed with hydrochloric acid (1 M) All collections of urine were performed under standardized dietary conditions (4)

Histamine (Hi) in the urine was measured by a bioassay technique according to Wetterqvist & White (19) and the values given are expressed as μg histamine base per 24

Table I *Pertinent data on 20 postmenopausal women in group 4*

A–K had no symptoms and treatment L–U had symptoms of hot flushes and/or sweats and were treated [illegible]
+ Hot flushes or sweats ++ both symptoms present (+) almost free from flushes and/or sweats 0 [illegible]

Subject	Age (y)	Parity	Weight (kg)	Smoking cigarettes/day	Time since menopause (y)	Symptoms	Symptoms after treatment
A	50	2	60	<10	3	0	
B	51	3	59	0	[illegible]	0	
C	51	2	64	0	3	0	
D	56	3	66	0	2	0	
E	57	1	70	<10	2	0	
F	58	3	65	0	1	0	
G	58	3	64	0	6	0	
H	60	2	64	<10	1[illegible]	0	
I	60	3	61	0	16	0	
K	65	2	65	0	10		
L	48	2	60	<10	2	++	( )
M	51	1	62	0	1	+	( )
N	52	2	59	<10	3	++	( )
O	54	0	66	0	3	++	(+)
P	55	0	65	0	1	++	( )
Q	56	0	60	0	3	+	0
R	57	3	61	0	5	++	( )
S	57	1	60	0	1	+	0
T	58	0	64	0	3	++	( )
U	58	2	64	0	4	+	0

hours corrected for recovery The identity of histamine was checked according to Reuse (15)

Methylhistamine (MeHi) in the urine was determined as described by Fram & Green (3) White (20) and Granerus et al (6) The values are given as μg methylhistamine base per 24 hours corrected for recovery

1 methyl-4-imidazoleacetic acid (MeImAA) in the urine was determined as described by Granerus & Magnusson (5) with slight modifications (4 11) corrected for recovery and expressed as mg per 24 hours

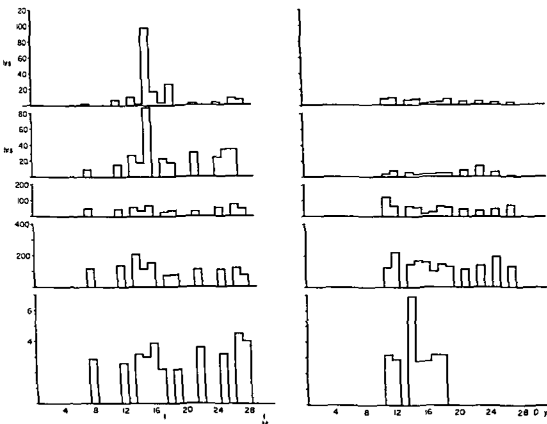
Excretion of luteinizing hormone (LH) in urine was measured according to a technique described by [illegible] Porath (22) Wide (21) and Wide et al (23) The values expressed in I U per 24 hours LH in serum was determined according to the same technique and expressed in ng per ml

The follicle stimulating hormone (FSH) in serum was determined according to Wide et al (23) and expressed in ng per ml

The total estrogen excretion was [illegible]

Table II *Urinary excretion of histamine (Hi) and methylhistamine (MeHi) in μg base per 24 h [illegible] cycles from six women taking oral combined contraceptives (group 1)*

Subject	Compound	Samples	Mean ±S E	Range	Tablet taken
A	Hi	5	46± 1	4?– 50	[illegible]
	MeHi	5	?46±?9	167–3?3	
B	Hi	5	14± 2	10– ?0	[illegible]
	MeHi	5	233±25	15?– 95	
C	Hi	5	16± 1	1?– 19	[illegible]
	MeHi	5	?30±35	1?0–334	
C	Hi	5	15±	15– ?0	[illegible]
	MeHi	5	?0±31	151–30?	
D	Hi	1	?3± ?	10– 38	[illegible]
	MeHi	1	?11±17	1?8–346	
E	Hi	5	16	10– ?1	[illegible]
	MeHi	5	?0? 3?	119–301	
F	Hi	4	36 8	1?– 65	[illegible]
	MeHi	4	1?6 5	110– ?1	



1 Urinary excretion of histamine (Hi) methylhista (MeHi) methylimidazoleacetic acid (MeImAA) es (Estr) and luteinizing hormone (LH) in a woman (age 26 one pregnancy non smoking) during one men strual cycle before (left) and (right) three months later during a period on oral contraceptives (Follinyl)

ing to the method of Brown (1) and Ittrich (8) and ues are given in μg per 24 hours

analyses in plasma were performed as de by Johansson (10) modified by Ellingboe et al (2) he analyses of e trogens and progesterone were as at the Department of Clinical Chemistry Sahlgren s pital

he first group of women Conlunett=norethisterone 1 + mestranol 0 1 mg Follinyl=norgestrel 0 5 mg + inylestradiol 0 05 mg Lyndiol mite=lynestrenol 2 5 mg tranol 0 075 mg Anovlar mite=norethisterone ace 3 mg + ethinylestradiol 0 05 mg Piloval=quingesta acetate 0 5 mg + ethinylestradiol 0 05 mg Astra −norethisterone 1 mg + ethinylestradiol 0 05 mg the second group of women Humegon=human l gonadotrophin (HMG) Pregnyl=human gonadotrophin (HCG)

In the second group of women Linoral=ethinylestradi 01 mg

stical methods

ventional statistical methods were used for the calcu of means and standard error of means (mean ±S E) Linear regressions were calculated according to the method of least squares

RESULTS AND COMMENTS

Six women on oral contraceptives excreted hista mine and methylhistamine in the urine (Table II) in quantities within the previously published limits of the normal menstrual cycle (4 11)

In nine other women where the subjects served as their own controls there were no differences in the mean urinary excretion of histamine and MeHi be fore and during treatment with oral contraceptives (Hi before treatment 37±5 μg/24 hours during treatment 32±4 μg/24 hours MeHi before 192±15 μg/24 hours during treatment 195±13 μg/24 hours) Fig 1 illustrates the excretion during one menstrual cycle and a period with oral contraceptives on one healthy female (the sixteenth) No significant changes in urinary histamine or MeHi were observed At one single day (the fi

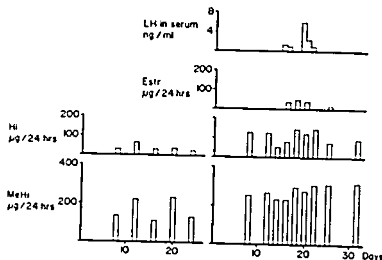


Fig. 2. Urinary excretion of histamine (Hi) and methylhistamine (MeHi) in a woman (subject F in Table II) studied during a period on oral contraceptives (Lyndiol mite, left). Twelve months later one menstrual cycle was examined when she had been without medication for [illegible] months (right). During this cycle estrogen excretion (Estr) in the urine and luteinizing hormone (LH) in serum were determined.

excretion of MeImAA rose substantially. This was preceded by a peak in histamine on the eleventh day and peak in MeHi on the twelfth day (right).

Fig. 2 shows on the other hand one woman (subject F in Table II) first studied when taking oral contraceptives (Lyndiol mite). She then stopped the medication and the investigation was resumed 12 months later. In this particular case there was a higher urinary excretion of both histamine and MeHi during the menstrual cycle.

Figs. 3–6 show the cases in group 2. Four women with secondary amenorrhoea were treated with human menopausal and human chorionic gonadotrophin during altogether eight periods. The doses injected are presented together with the excretion values of hormones and histamine and metabolites in the figures. The excretion levels of plasma progesterone verified ovulation on all occasions.

Three of the patients seemed to react in the same manner. They showed a tendency to increased urinary output of MeHi in parallel with increase [illegible] estrogen excretion (Figs. 3 and 4). After the maximal estrogen response had been reached there was a decrease in the MeHi values. As shown in Fig. [illegible] subject excreted increasing amounts of [illegible] and MeImAA in parallel with an increased [illegible] estrogen excretion. A subsequent decrease [illegible] observed immediately after the period of [illegible]tion. However, in a second course of gonadotrophin stimulation of subject 3 no significant [illegible] MeHi output in connection with the [illegible] could be observed (Fig. 4 right and Fig. 5).

The fourth patient (Fig. 6) reacted with [illegible] urinary excretion of histamine but not of [illegible] MeImAA. In a second attempt to [illegible]tion there was a weaker hormonal response [illegible] slight if any increase in urinary histamine.

Fig. 7 and Table III show the results [illegible]

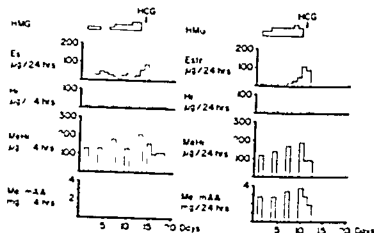
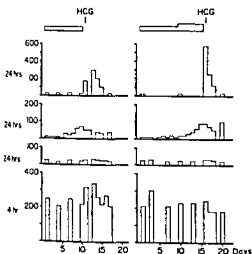


Fig. 3. Urinary excretion of histamine, methylhistamine (MeHi) and [illegible] acetic acid (MeImAA) and estrogens [illegible] in subject 1 (left) and subject [illegible] secondary amenorrhoea [illegible] 1 was treated with human menopausal gonadotrophin (HMG) [illegible] daily—as indicated at the top [illegible] Subject 2 was treated with doses of [illegible] or 300 I.U. daily. At the peak [illegible] the arrow both women were [illegible] 9000 I.U. of human chorionic gonadotrophin (HCG).



4 Urinary excretion of histamine (Hi) methylhista (MeHi) estrogen (Estr) and luteinizing hormone) in subject 3 with secondary amenorrhoea (group 2) reated during the first period (left) with 150 I U nan menopausal gonadotrophin (HMG) daily and ng the second period (right) with doses of 150 or ?25 daily as indicated at the top of the figures At the marked by the arrows she was injected with 9000 of human chorionic gonadotrophin (HCG)

nts in the ?0 postmenopausal women in group 3 mean excretion values for histamine and MeHi ie group were within the normal limits previ ly published for fertile women (4 11) and no ces were found between the subjects with those without symptoms The 10 women with oms were then given estrogen orally each day at least four weeks while the other 10 received treatment There was a slight positive correla between the excretion values for estrogen and urinary histamine in the symptom free untreated up (r=0 58) (Fig 7 left) Estrogen treatment did alter the urinary excretion of histamine and Of the hormones analysed only FSH showed ecrease and this observation together with the ical improvement indicated that the dose given adequate

DISCUSSION

current study illustrates the difficulties in lved in trying to understand the role of female sex in histamine metabolism in man Firstly is obvious that there are large individual varia in excretion values of histamine and MeHi in women without abnormal changes in the internal secretion of sex hormones It is known that the methodological error is on average ±10% for the analyses of histamine and MeHi (Wetterqvist unpublished)

Secondly there is an upper limit for the ability of a subject to cope with an investigation of this type More samples from more women would have been desirable but this was not possible for practical reasons

Thirdly the processes underlying the turnover of female sex hormones in the body are not yet fully understood We have not included studies of releas ing factors in our schedule nor did we analyse adrenal secretions The possibility also remains that the histamine turnover may affect the secretion of female sex hormones via a local or general feedback mechanism

Fourthly the principles for the regulation of the total histamine turnover in man are largely un known The importance of the composition of the food ingested for histamine metabolism is undisput able (4) but the functional state of the gastrointesti nal tract (17) as well as physiological changes in the kidneys may also be of some importance

Green et al (7) found increased values for hista mine and/or MeHi in the urine of two amenorrhoeic patients in whom an increase in the endogenous estrogen levels had been induced by administration

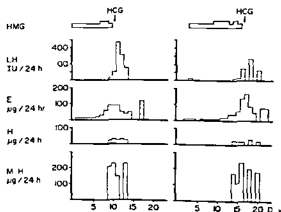


Fig 5 Urinary excretion of histamine (Hi) methylhista mine (MeHi) estrogen (Estr) and luteinizing hormone (LH) in subject 3 with secondary amenorrhoea (group 2) during two further periods of hormone stimulation During these periods she was treated with 150 or ?25 I U of human menopausal gonadotrophin (HMG) daily as indi cated at the top of the figures At the points marked by the arrows she was injected with 9000 I U of human chorio nic gonadotrophin (HCG)

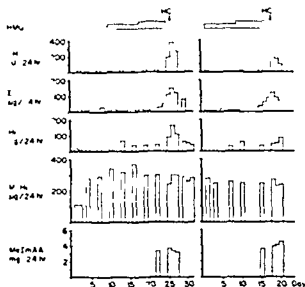


Fig 6 Urinary excretion of histamine (Hi) methylhistamine (MeHi) estrogen (Estr) and luteinizing hormone (LH) in subject 4 with secondary amenorrhoea (group 2) during two periods of hormone stimulation She was treated with 75 150 or 225 I U of human menopausal gonadotrophin (HMG) daily as indicated at the top of the figures At the points marked by the arrows she was injected with 9000 I U of human chorionic gonadotrophin (HCG)

of gonadotrophic hormones The changes in MeHi values were not impressive whereas the histamine tended to increase However there did not seem to be any absolute correlation between high estrogen values and a high urinary histamine output nor did Green et al collect urine under standardized dietary conditions

Previous results from this department showed a obable correlation between the endogenous estrogen levels and histamine turnover in that histamine MeHi and MeImAA excretion increased at midcycle (11) The present study seems to support this observation Stimulation of amenorrhoeic women with gonadotrophin inducing a marked increase in the endogenous estrogen levels resulted in a slight augmentation of histamine and/or metabolite output in 4 of 8 trials Oral contraceptives (estrogen or gestagen dominated) did not influence histamine turnover significantly A similar lack of effect was found in the guinea pig (14) whereas a combination of estrogen and progesterone increased histamine output in the mouse (13) and decreased the excretion in the rat (12)

These findings illustrate marked differences in histamine turnover between different species It should however be born in mind that the oral contraceptives represented a long lasting medication whereas the animals were subjected to a hormonal stimulation by single injections The mechanism behind the steroid induced effect on histamine turnover in the human female is difficult to explain It has been shown that estrogen effect on histamine depletion in the uterine tissue of ... It seems however not probable that only local alterations within the reproductive organs may be reflected in the urinary output of histamine ... mast cells are presented in nearly all tissues throughout the human body

Climacteric symptoms are mainly characterized by the occurrence of hot flushes and sweats The pathogenesis of this syndrome is not ... understood It has been suggested that the vasomotor symptoms should be the result of an imbalance between the hypothalamus and the ... nervous system brought about by a decrease of estrogen Hot flushes in the same region of the ... can be induced by intravenous injection of histamine and it could be speculated that this substance might be involved in the pathogenetic events

The present results show that there is no difference in the excretion of histamine and MeHi between postmenopausal women with and without climacteric symptoms Nor is there a ... in this respect between postmenopausal and ...

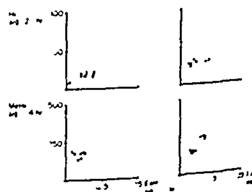


Fig 7 Urinary excretion of histamine (Hi) methylhistamine (MeHi) and estrogen (Estr) in 10 women ... menopausal age without any symptoms of climacteric ... in 10 other women of the same age but with ... hot flushes and ... sweats ... obtained without any treatment ... obtained when the women were treated ... diol (20 μg daily)) (Left upper part ...

able III *Urinary excretion of histamine (Hi) and methylhistamine (MeHi) in µg base per 24 hours in 20 ›pausal women (group 3)*

ıe first 10 (A–K) had no symptoms and treatment The others (L–U) had symptoms of hot flushes and/or sweats and ɹe treated with ethinylestradiol at the time of the second urine collection (.0 µg daily)

bject	Compound	Samples	Treatment	Mean ±S E	Range
	Hi	0	No	⁷8± 3	10– 49
	MeHi	⁷0	No	197±16	9 –354
	Hi	20	No	.7± 2	10– 46
	MeHi	0	No	.02±19	76–364
U	Hi	19	No	22± 3	7– 59
	MeHi	19	No	192±11	109–.89
	Hi	⁷0	Yes	23± 4	7– 88
	MeHi	0	Yes	195±15	110–⁷47

n (11) It is hard to believe that the probable ear distribution of the histamine excretion values the symptom free women as compared to the ᵏ of linearity in patients with symptoms has any ıngful significance It has been observed that ɹents undergoing cryotherapy for premalignant ıcal lesions get temporary hot flushes during thawing of the cervical tissue Measurement of nary histamine and MeHi showed an increased ɹion for at least four hours following the ɜtment (18) It seems probable that post ›pausal hot flushes are not elicited by a emic release of histamine into the circulation

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EXPOSURE TO DRUGS AND OTHER POSSIBLY HARMFUL FACTORS DURING THE FIRST TRIMESTER OF PREGNANCY

Comparison of Two Prospective Studies Performed in Sweden 10 Years Apart

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ct 474 women in mid pregnancy interviewed at different hospitals in Sweden were questioned on a ber of social and medical items e g drug use con ceptive technique used before pregnancy exposure to sibly deleterious factors in the environment The dy compared with a similar study made ten years lier in Sweden showed little or no difference in the use iron and/or vitamin preparations analgesic drugs biotics or endocrine drugs but a drastic reduction is ed in the use of psychotropic drugs and of histaminic drugs A marked decrease in frequency of t trimester X ray exposures can be found but no ked changes in smoking habits Appr 18% of the men used contraceptive pills within 6 months of becom pregnant—3 had used them during early pregnancy out 4% (18 women) had used IUD—one became preg t with a Cu IUD (intra uterine device impregnated h copper)

This type of study can provide some information on the valence of relatively common factors but it must be siderably extended in order to permit an analysis of events e g use of most drugs

ring recent decades much interest has been wn in the possibility that exogenous factors can mage the developing human embryo with bryonic death or maldevelopment as a result us diseases drugs smoking and exposure to ironmental pollution are factors with such po- tials Various surveillance systems have been roduced for detecting changes in malformation es and for identifying harmful factors In order to aluate such information knowledge of the preva ce of various possibly harmful factors among gnant women is needed

Obviously the use of drugs and other exogenous tors can vary considerably between different countries in different populations within a country and with time Knowledge of such data could help to strengthen or weaken supposed correlations be tween a specific factor and the occurrence of a specific malformation Some efforts have been made to collect this type of information—a much quoted study is that by Nora et al (11) where 240 pregnant American women were questioned during pregnancy a mean number of 3 7 potentially teratogenic factors was found per woman

The present study compares the results of two prospective investigations into exogenous factors during pregnancy Both were performed in Sweden with an approximately 10-year interval The two studies were designed differently and were performed with somewhat differing aims This must be borne in mind when comparing the results

The older study—Study 1—performed in 1963–65 tried to analyse the total population of pregnant women in one city Malmo during a specified period Nearly 6400 pregnancies were studied and all data obtained during the *whole* of the pregnancy were collected Some reports from this study have been published (1 5–9)

The more recent study—Study 2—performed in 1973–74 studied a sample of women from ten differ ent hospitals distributed throughout the country From each woman information was obtained only once It referred mainly to events during the first trimester The information required was thus only part of that sought in Study 1 However Study 2 raised two points not included in Study 1 (*a*) con cerning contraceptive measures taken during a period of 6 months before pregn (*b*) co

Table I *Specification of items included in questionnaire in Study 2*

Date of interview age of interviewed woman civil status
Date of LMP and number and year of earlier pregnancies and their outcome
Diseases asthma epilepsy diabetes heart disease
Contraception technique used during 6 months before pregnancy
Vaccination within 3 months before and 12 weeks after LMP
Information concerning first trimester
Place of residence work outside home possible noxious exposures in home environment or at work Profession of spouse Smoking habits Is the pregnancy wanted?
Morning sickness no very little yes very much
Bleeding since LMP no single small many small single large many large
Diseases since LMP
Contacts with contagious diseases
Operations performed under complete anaesthesia
X rays performed
Use of drugs including homeopathic drugs kind time when used dosage total amount indication for drug
Other information of interest e g peculiarities in diet exposure to certain poisons (insecticides pesticides) accidents etc

cerning possible exposures to environmental factors that the woman thought could be harmful to the unborn child The primary aim of Study 2 was to make a pilot investigation in order to find out whether it is possible in that way to form a sampling network which could supply information on the presence and significance of various exogenous factors with the main stress on drugs that could be noxious to the embryo

MATERIAL AND METHODS

Study 1 is a prospective study carried out during 1963–65 in the city of Malmö 6376 women (92 3% of all pregnancies during that period) were interviewed when they sought medical advice because of pregnancy outside or inside the hospital The loss is not random 4 7% were supposed to be included but refused to co-operate 2 9% *were not included for undisclosed reasons* There is an over representation among the non included women of those who would go on to have a legal abortion To make comparisons with Study 2 more meaningful the present study comprises only those who continued their pregnancies to childbirth i e 5678 women repre[senting] 92 4% of all women who—pregnant during the period—gave birth in Malmö

Information was obtained mainly through a s[...] questionnaires completed during the entire period [...] nancy by the woman sometimes with the help [...] doctor she attended These data were supplement[ed] data from other sources mainly from hospital recor[ds] such data concerned first trimester conditions on[ly to a] small extent

Study 2 was performed during the second half [...] and the first half of 1974 It involved ten different [hospi]tals[1] fairly well covering the country geographica[lly] each hospital one or several midwives selected [...] *terviewed approximately 50 women who attend[ed]* outpatient departments during the second half of th[e preg]nancy One hospital interviewed only 15 women [...] and the rest between 50 and 67 The actual me[...] month when the interviews were made varied bu[t a] total of 474 were performed after the first trimes[ter] before childbirth

Table 1 summarizes the questions in these inte[rviews] Personal instructions were given to all midwives wh[o took] part in the study in order to explain the aim and t[...] any difficulties of definition The co operation fro[m mid]wives was excellent and we express our sincere th[anks to] them all for their contribution

The outcome of the 474 pregnancies was chec[ked] could not be identified however Four had ended [in] miscarriage (one of them had a hydatidiform mo[le]) [For] comparisons with results from Study 1 these te[n were] excluded and only the remaining 464 pregnancies [known] to have ended in childbirth were used

RESULTS

1 *How representative are the groups studied?*

In Study 1 more than 90% of all women who [gave] birth in Malmö during the period involved [took] part The excluded cases deviated somewhat [with] respect to age and nationality for instance [...] the less the included group must be regarde[d as] reasonably representative of women that [gave birth to a] child in Malmö during the period involved [How]ever it might differ from the total populati[on of] such women in the country as a whole It is pos[sible] to compare the Study 1 sample with the [...] country with respect to age distribution and [civil] status as these data are available from the Swe[dish] official statistics Study 1 group population dev[iates] markedly and significantly with respect to age [dis]tribution with an increased percentage of wo[men] below 20 years or above 35 years of age (Fig [1]) $\chi^2=68.9$ $P<0.001$ The agreement with respec[t to] civil status is good (Fig 2) $\chi^2=0.78$ N S

[1] Sahlgrenska sjukhuset in Gothenburg the hospitals of Karlstad Kristianstad Luleå and Malmö Sabbatsbergs and St Eriks sjukhus in Stockholm and the hospital of Sundsvall Umeå and Vaxjö

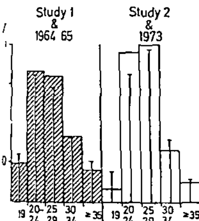


Fig 1 Diagram showing age group distribution—as percentages of the total material—in Study 1 (▨) and Study 2 (□) The percentages valid for each age group in the total material of all births in the country are marked with vertical lines

Study 2 compared with the total population of childbearing women in all Sweden during 1973 also ... lated with respect to age distribution (Fig 1) ... e information having been collected at ten ... sites $\chi^2=16.7$ $0.01>P>0.001$ Again the ... ibution of women below 20 years of age was small A deviation is found also with respect to status (Fig 2) The percentage of married ... is lower in the Study 2 group than in the ... d material ($\chi^2=15.9$ $P<0.001$) The study 2 material probably reflects a mainly urban population ... reasonably large hospitals were included in the ... v four of them situated in large cities

As age and civil status influence drug use and ... y other similar features the data obtained must ... interpreted carefully

Changes in age distribution and ... d status

Comparison of the 1963–65 data with those of ...3–74 shows a marked difference in age distribution at childbirth in Sweden fewer women now ... children before 20 years age (12 5% and 7 5% p) and also after the age of 35 (10% and 6% p) This difference is further accentuated when ... two *study samples are compared* A marked reduction has taken place especially for the age group below 20 from 10% in Study 1 to approx 3% in Study 2 The actual difference in age distribution between the two studies is statistically highly significant ($\chi^2=35.6$ at 4 d f $P<0.001$) When markedly age dependent features of the two studies are compared a correction for the difference in age distributions should be taken into account

Fig 2 compares civil status This comparison is complicated by a shift in matrimonial habits during the decade As seen in Fig 2 31% of the women inviewed in Study 2 said they were unmarried but lived together with the infant s father in a marriage situation but without society s formal sanctions The corresponding group in 1963–65 was probably negligible and was never identified in Study 1 Fig 2 suggests that this civil status is most comparable to an actual marriage situation The sum of numbers of married couples and couples cohabiting without formal marriage (= unmarried couples) even somewhat exceeds the group married in Study 1

Another aspect of the socio medical significance of the different civil status groups can be obtained by studying the incidence of wanted pregnancies in the different groups

Fig 3 illustrates the findings In the Study 1 material approximately 92% of all women that were married when they become pregnant positively stated that their pregnancies were wanted Naturally the percentage of wanted pregnancies was much lower in the group of women that were not married at the beginning of their pregnancy and a considerable percentage of such pregnancies ended in an *induced abortion therefore 67% of women belonging* to this category who continued their pregnancy to childbirth had during pregnancy reported that the pregnancy was wanted

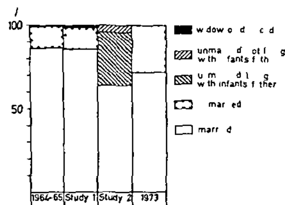


Fig 2 Diagram comparing distribution of civil status groups in Study samples with the total of births in the country

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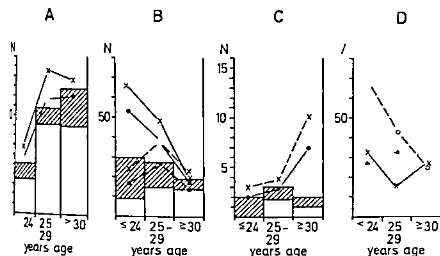


Fig 5 Diagrams showing found numbers (N) of live births (□) and pregnancies ending with other than live births (hatched columns) and also civil status of different age groups in Study 2 A married women B unmarried couples C unmarried single In each Figure the expected numbers from Study 1 are marked ×—× total number of pregnancies ●—● number of live births from the group married at LMP in Study 1 dashed lines give the corresponding numbers from the group unmarried at LMP Study 1 D shows the percentage of pregnancy wastage for each civil status group and each age class ×—× married O--O unmarried couple Δ Δ unmarried single

this group From the group married at LMP in Study 1 132 were expected from the group unmarried at LMP 80 were expected In Study 2 39 live births were found—from the group married at LMP 108 were expected and from the group unmarried at LMP 58 were expected Thus from the standpoint of earlier reproduction this group resembled best the group unmarried in Study 1 especially if a general reduction in the number of pregnancies is taken into account such as is seen when the married groups of the two studies are compared

Fig 5 compares the expected and found numbers of pregnancies and live births at different civil status and age For the married group no great differences for different age classes exist in the relation between the two studies For the group unmarried couples the main deviation is found within the youngest age group (below 20 years)—for the age group above 30 years no actual differences were found between the studies For the group unmarried single the most marked difference is found for the age group above 30 years

Fig 5 also shows the percentage of previous pregnancy wastage in different age groups and for different civil status categories The most deviating group is that of unmarried couples especially in the age group 20 years Their rate of earlier legal abortion is twice that of the other groups 6 out of 30 earlier pregnancies against 26 out of 346

4 *Contraceptive technique used before pregnancy*

Fig 6 summarizes data on contraceptive technique used 6 months before pregnancy based on all 474 pregnancies in Study 2 The A diagrams show the percentage of women reporting that no contraception was used It hardly varies with age civil status or whether the pregnancy was wanted—the small recorded differences are only indicative as the material is not very large a slight increase in this percentage occurs with age and a somewhat higher incidence among women who report a wanted pregnancy than among those who report an unwanted pregnancy

On average 52% of all women report that they used no contraception during the 6 months preceding the present pregnancy

Of the 228 women who used some sort of contraception during this period 87 (38%) used the Pill and in 112 cases (49%) the partner had used condoms 18 (8%) women had an intra uterine device only 4 (2%) had used a vaginal diaphragm The other 7 had used various techniques including

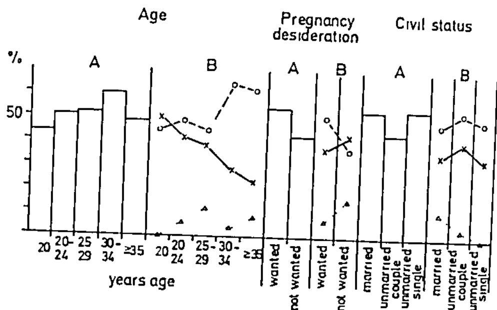


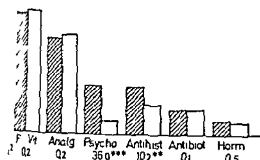
Fig 6 Diagrams showing percentage of women who did not use any contraception for 6 months before becoming pregnant (A diagrams) and its variability with age pregnancy desideration and civil status B diagrams show the percentages using the Pill (×—×) condoms (O--O) IUD (Δ Δ) among women using some contraception Division according to same variables

only chemical means and interrupted coitus One woman using a Cu IUD became pregnant despite the device The B diagrams in Fig 6 show distribution of the three main contraceptive techniques as a percentage of all women taking some sort of precautions according to age civil status and whether the pregnancy was wanted The most obvious variation occurs with age with increasing age the use of the Pill decreases with a corresponding rise in the use of the other two techniques especially of condoms The three variables age wanted pregnancy and civil status co-vary considerably but the material too small to permit a study of the contribution of each source of variation So far however no data argue against the hypothesis that age is the dominating and perhaps the only decisive factor With that hypothesis the maximum recorded deviation between found and expected numbers is 2 8—in the group unmarried couples not wanted pregnancy 5 2 expected and 8 found This could well be random

5 *Drugs used during the first trimester*

Six different groups of drugs were compared in the two studies iron and/or vitamin preparations analgesic drugs antihistamine drugs mainly used as antiemetics psychotropic drugs antibiotics and chemotherapeutic agents such as sulphonam and hormones The percentage of women using or more drugs belonging to each of these categ was known from Study 1 (most of these data published in Refs 6–9) and was determined Study 2 in the following way In most instances first month during which a specific drug was ta was reported A drug reportedly used for the f time during the first trimester was called a f trimester drug Some reports did not explic state when a drug had been used—this was es cially true for iron and/or vitamin preparations for analgesics

117 women stated that they had used iron and vitamin preparations during the first trimester in other cases the time of drug use was not know The highest possible number of women using su drugs during the first trimester was thus 182 (39% and the lowest possible number was 117 (25%) 1(women reported the use of these drugs during som part of the pregnancy (thus also after the fir trimester) therefore 117 (72%) of them had begu drug use during the first trimester If this figure valid also for those women that did not state th time of drug use 72% of 65 women were also firs trimester users making a total of 164 (35%) This estimate is regarded as the most probable one obtainable from Study 2



7 Drugs used during first trimester expressed as all women who on one or more occasions ed drugs belonging to different groups as shown by ubscript Fe Vit=iron and/or vitamin preparation ug analgesic drugs Psycho=psychotropic drugs st=antihistamine drugs Antibiot=antibiotics or utic agents Horm=endocrine preparations Study ? χ^2 values compare the two studies 01>P>0 001 P<0 001

similar calculation was made for analgesics 89 (19%) reported having used analgesic drugs the first trimester and a further 50 did not when the drug was used making a maximum 30%) The most probable number—calculated described for the iron and vitamin prepara 130 (28%)

Fig 7 compares the first trimester drug use in udy I with Study 2 For iron and vitamin prepara analgesics antibiotics and hormones no dif is found between the two studies but a and significant reduction in the use of otropic drugs and antihistamines can be The latter two types of drugs are used with fferent frequency according to the desire for egnancy (6 7) In Study I thus 12 7% of women porting a wanted pregnancy used psychotropic but 23 3% of women reporting a un wanted gnancy If these figures are used to estimate the number of drug users in Study 2 where 3 women reported a wanted pregnancy 65 first mester psychotropic drug users are expected only 16 were found ($\chi^2=36$ 9 at 1 d f $P<0$ 001) The most frequently used psychotropic drugs in 1 were barbiturates meprobamates and lordiazepoxide In Study 2 the following drugs recorded chlordiazepoxide (4 women) am (3 women) nitrazepam barbiturate lorprothixene ethchlorvynol amitriptyline nor tyline

In Study 1 72% of all women who later gave birth complained of morning sickness of varying degree during pregnancy The corresponding percentage in Study 2 is 71% The reduced inci dence of antihistamine use found in Study 2 com pared with Study 1 thus cannot be explained by different frequency of morning sickness complaints The following antihistamine drugs were used in Study 2 promethazine (18 women) meclizine (10 women) diphenhydramine prochlorperazine (each one woman) meclastine (3 women) dex bromphenitamine cinnarizine (each one wo man)—the three last mentioned drugs are used for allergic complaints In Study 1 the three most used drugs were promethazine prochlorperazine and diphenhydramine

In Study 2 33 women reported that they had been given antibiotics or chemotherapeutic agents during the first trimester—38 different prescriptions had been made In all except one the indication was an infectious disease—the exception had penicillin as prophylaxis after contact with scarlatina Table II sums up the diagnoses 13 patients (about 3%) had urinary tract infections during the first trimester This is more than was recorded in Study 1 (less than 1%) and is reasonably due to increased awareness of the complications of urinary tract infection dur ing pregnancy leading to earlier detection Seven of these patients were treated with sulphonamides on ly 3 with nitrofurantoin and 3 with a combination of both drugs Ten patients thus had sulphonamides —the rate of first trimester use of this drug in Study 1 (cf 9) was 2 3% At this rate 11 patients in Study 2 had used the drug

Ten patients in Study 2 used penicillin during the first trimester mainly because of upper respiratory infections The expected number from the rate re corded in Study 1 (3 2%) is 15

In Study 2 endocrine drugs given during the first trimester were reported by 16 women Three of them had continued with oral contraceptive pills during the first part of the pregnancy Eight had gestagens This figure compares well with the 2% found in Study 1 Four of the 8 women who took gestagens reported bleeding during early pregnan cy the other 4 had previously had one or more miscarriages Seven of the 8 women were treated at one and the same hospital from where 54 reports were obtained Among them 10 had an earlier mis carriage (one had had two) and 4 of the 10 had gestagens A further 8 had bleeding during pregnan cy 3 of them had taken gestagens Among the 410

Table II *Infectious diseases reported in Study 2 during the first trimester and use of antibiotic (or chemotherapeutic) drugs*

Diagnosis	No of patients	No using antibiotics	No of diagnoses
Common cold	63	9	64
Otitis sinuitis	3	3	3
Tonsillitis	8	5	8
Influenza	22	5	22
Virus disease	1	0	1
Subtotal all upper respiratory tract infections	*97*	*22*	*98*
Enteritis	5	2	5
Urinary tract infections	13	13	13
Vaginitis	1	0	1
Skin infection	1	1	1
Total	*110*	*33*	*118*

women interviewed at other hospitals 54 had one or more earlier miscarriages—none had taken gestagens 65 reported bleeding during pregnancy—only one had taken gestagens she had repeated slight bleeding but no previous miscarriage

In Study 1 16 6% of women who later gave birth reported bleeding during early pregnancy (cf 8) and almost the same incidence was found in Study 2 73 women (16%) Of these only 8 had the formal diagnosis of threatened abortion Together these 8 women had three earlier pregnancies two of which ended in miscarriages Out of the total material only 19% of earlier pregnancies ended in miscar

Smoking X rays and vaccinations during pregnancy

Fig 8 compares the two studies with respect to the occurrence of smoking X ray investigations and vaccinations during the first trimester

Smoking habits have changed little In Study 1 (cf 5) 41 6% of women that later gave birth smoked during pregnancy—in Study 2 this would mean 193 187 were found Among the smokers a shift had occurred towards more cigarettes smoked per day (cf Fig 8) If the three groups are compared between the two studies (non smokers smoking less than 10 and smoking more than 10 cigs/day) the difference appears significant $\chi^2=9\ 8$ at 2 d f $0\ 01>P>0\ 001$

The incidence of diagnostic X ray investigation performed during the first trimester is lower ir Study 2 than in Study 1 In Study 1 6% of the women had a dental X ray performed during tha period—this would correspond to ?8 women i Study 2 but only 9 were found ($\chi^2=1?\ 9$ at 1 d f $P<0\ 001$) Chest X rays had been taken in 5% i Study 1 this would correspond to 23 women i Study 2—only 8 were found ($\chi^2=9\ 8$ at 1 d f $0\ 01>P>0\ 001$)

The most common vaccination registered ir Study 2 was for smallpox Seven women had beer vaccinated during the first trimester and a further within 3 months before their pregnancies In Study 1 1 8% of the women and been vaccinated for smallpox during the first trimester this would correspond to 8 women in Study 2

7 *Miscellaneous*

In Study 2 the women were asked to mention posures during the first trimester—at work or home—to factors that could be thought harmful the unborn child and also to peculiarities in th diet 222 women (47%) mentioned such factors a a total of 269 exposures were detailed together w 9 dietary peculiarities Table III summarizes former data arbitrarily grouped A total of ?0? posures at work were thus mentioned and 67 posures in the home environment or otherwise o side the working place One large group is exp sures to contagious diseases during work work hospitals or other medical work service jobs le ing to frequent contact with a large number of pe ple and work with children in schools etc Amo the many other items mentioned is exposure paints and organic solubles—35 women (7 mentioned this Five women reported work operating theatres which means possible expos to leaking volatile anaesthetics X ray work reported by 11 women and work with radioacti isotopes by 4 Among the dietary peculiariti blighted potatoes was mentioned once

The number of recorded exposures could to so extent be related to the interview technique Wh the number of women giving information on the points was compared between the different hos tals differences were found The lowest frequen recorded was 15 out of 56 interviewed (27%) t highest 34 out of 50 interviewed (68%) A χ^2 test f heterogeneity in reporting frequency between t hospitals gives $\chi^2=30\ 5$ at 9 d f $P<0\ 001$

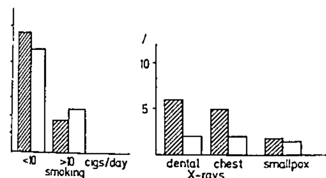


Fig 8 Diagrams showing percentages of women who smoked or were exposed to first trimester X rays or first trimester smallpox vaccination ▨ data from Study 1 □ from Study 2

Malformation and perinatal death
Study 2

e material in Study 2 is too small to give mean l information on specific factors related to ormations or perinatal death Table IV sum the outcome of the pregnancies with stress abnormalities and infant death This information y based on the neonatal records submitted birth registration (sometimes supplemented with from hospital records) and is therefore prob ly incomplete It cannot be directly compared data from Study 1 (1) as those records on in abnormalities were more detailed There were remarkable first trimester occurrences in the that ended with abnormal births in 2

DISCUSSION

human embryo is exposed to various possibly ious influences of exogenous origin Some have initely injurious effect e g maternal smoking 5 10) the deleterious effect of other factors most drugs is hypothetical A comparison of of exposures in the two studies reveals differences Smoking has not markedly de ed during the intervening ten years between two samples if they represent the smoking s of the total Swedish population of pregnant n Perhaps Study 1 overestimated the smok habits in the mid sixties as this sample was from a purely urban population The re efforts to reduce smoking by information apparently had little effect on this important et group pregnant women

No definite harmful effect on the embryo can be ibed to analgesic drugs (cf Discussion in 9) when used in moderation None the less various possibly deleterious effects including teratogenici ty have been widely published even in the lay press Despite this no decrease in frequency in the use of analgesic drugs has occurred

By contrast a definite decrease in exposure to psychotropic drugs and antihistamine drugs can be recorded The same is true of X ray exposures All are more or less governed by medical advice and the (unproved) possibility of harmful effects on the embryo can have contributed to an increased cau tion in their use in first trimester pregnancy There has been a general restriction in the use of psycho tropic drugs in Sweden during this period No de crease of a comparable size in the use of antibiotic drugs or endocrine preparations can be found The latter group however demonstrates the inherent risk in such comparisons Out of the ten hospitals studied one issued nearly all prescriptions for gestagens If that hospital had not taken part in the study it could easily have been concluded that such drugs are no longer used during pregnancy to pre vent a threatened abortion

This raises the issue of how representative the samples are The Study 1 sample can be regarded as representative of the population of pregnant women in Malmo during this period as 92% were included but it deviates with respect to age distribution from the total population of child bearing women in Sweden Data on drug use obtained from the Study 1 sample can markedly deviate from the general drug use—and it most probably does! In Study 2 an effort was made to overcome this source of error by distributing the interviews among ten different hospitals throughout the country The above de scribed example with gestagens shows that this ef fort can easily fall short of the ideal The skew

Table III *Exposures of various exogenous factors mentioned by interviewed women in Study 2 (all interviews)*

Group	Subgroups	Exposures At work	Exposures At home	Total of exp wome
Exposure to contagious diseases	Work in medical care	59		
	Service jobs	37		
	Work in child care	28		125
	Work with animals	1		
Exposure to possibly harmful chemicals	Paints solubles	14	21	
	Insecticides pesticides ets		12	
	Laboratory chemicals	8		63
	Hair sprays etc	3	2	
	Volatile anaesthetics	5		
	Solder smoke	1		
Exposure to a generally poor milieu	Car exhausts	2	20	
	Poor ventilation and noise	4		26
	Work in smoky rooms	1		
Physical strain or trauma	Heavy lifting	11		
	Violence accidents	1	4	18
	Animal bites		2	
Psychological trauma	Stress at work	12		18
	Grief etc		6	
Exposure to ionizing irradiation	Work with X ray	11		
	Work with radioactive isotopes	4		
Totals		202	67	217

distribution found in age and civil status is also a bias Its origin can lie in the selection of hospitals —leading for example to an over representation of urban populations—but it can also be the result of an unintended selection of women for interview Whatever bias is obtained in Study 2 the recorded data can give a rough estimate of the efficiency of this type of data collection system

If the data are collected to identify women who have used specific drugs during early pregnancy in order to search for teratogenicity the study must in most instances be considerably extended Except for a few quite common drugs (e g chlordiazepoxide diazepam meclizine promethazine) only isolated records of drug use were found in this sample of 474 persons To obtain material large enough to make analysis for teratogenic effects meaningful possibly ten times as much data is needed

If the two study samples are at least reasonably representative of the drug use by pregnant women in Sweden during two periods ten years apart some comments can be made on changes in drug use The use of psychotropic drugs during the first trimester has been markedly reduced perhaps to a quarter If the figures obtained in Study 1 are representativ the entire country possibly 15000 women u such drugs during the early part of pregnancy e year in the mid sixties If the Study 2 figures also representative of the 1973 situation number has been reduced to possibly 4000 elimination of perhaps 10000 first trimester ex

Table IV *Summary of offspring in the 464 pr nancies*

Total number 464	
Live born 458	
Stillborn 6	
Abnormalities recorded 15	
Down s syndrome	1
Anencephaly	1
Hypospadias	1
Syndactyly	1
Persistent ductus arteriosus	1
Heart murmur (no final diagnosis)	1
Pes equino-varus	1
Pes calcaneo valgus	3
Preluxation of the hip	1
Preauricular appendix	1
Undescended testis	1
Imperforate hymen	1
Penis recurratum	1

ures to psychotropic drugs has in no detectable ay reduced the incidence of malformed infants orn in the country (cf 2) The reduction in anti istamine use is less marked but—calculated in the ame way—could perhaps represent 5000 exposures

Little is known about the possibly harmful effect chemicals in the everyday life on the development of the human embryo The information tained in Study 2 and detailed in Table III on ich matters probably mainly reflects the prehensions and suspicions held by the interviewer and the interviewee This is further supported by the significantly variable amount of information obtained by different interviewers in different hospitals

Some of the recorded factors have been more or ss seriously discussed in the scientific literature teratogenesis e g ionizing irradiation (cf 12) olatile anaesthetics (3) organic solubles (4) blight potatoes (13) others have been much discussed ublically e g insecticides and pesticides others rry a long standing bad reputation among laymen g heavy lifting and psychological stress

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SERUM HUMAN PLACENTAL LACTOGEN (HPL) LEVELS IN PATIENTS WITH INTACT HYDATIDIFORM MOLE

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Serum human placental lactogen (HPL) levels in ...ty cases of intact hydatidiform mole were measured by ...unoassay The HPL values were generally lower ...normal pregnancies of the corresponding period of ... However normal and occasionally higher than values were observed in a few cases Serum HPL ...ne is of some clinical use in the diagnosis of hyda...form mole When combined with human chorionic ...opin (HCG) a low HPL/HCG ratio for the cor... period of amenorrhoea is a useful index in the ...s of hydatidiform mole

...he production of human chorionic gonadotropin ... human placental lactogen are inherent pro...ies of the trophoblast in all its forms—normal ...lacenta, hydatidiform mole and choriocarcinoma ... placental lactogen (HPL) is produced by the ...ytoplasm of the placental syncytiotrophoblast (14) ...he presence of HPL in the sera of patients with ...lastic tumours is of interest as it provides ... possible endocrine index of following the ...nction of these tumours

Earlier studies on the level of HPL in hydatidi... mole have produced contradictory results ...rumbach and Kaplan (5) first reported high levels ... a case of hydatidiform mole Similar low HPL ...alues in hydatidiform mole were reported in other ... by Frantz et al (2) Samaan et al (11) Yen ...al (10) Saxena et al (13) Chough (1) and Sato ...) Values were thought to be invariably low ...ome 10–100 times below the normal expected ...els for the corresponding gestational age In ...ition the HPL levels were well below the range ...of an early normal pregnancy of less than 10 weeks ...tational age Subsequently Goldstein (4) re...rted HPL levels in 94 cases of unevacuated molar ...ies He noted a wide range of serum HPL values from those consistent with a normal pregnancy to 10–100 times below the normal expected values for the corresponding gestational age (See Table I)

The present study was done to evaluate further the significance of the observed abnormality in serum HPL in patients with intact molar pregnancies The potential value of HPL as a useful adjunct in the endocrine diagnosis of molar pregnancy was investigated A subsequent study will deal with sequential assay of serum HPL during the course of choriocarcinoma to determine its usefulness as an index in the management of the disease

MATERIAL AND METHODS

All cases of hydatidiform mole were seen by the same mole team Only cases of intact molar pregnancy were included in this study The criteria of selection were (*a*) There must be no passage of molar vesicles per vaginum Spotting per vaginum was acceptable since the majority

Table I *Cummulative data on serum HPL in patients with hydatidiform mole*

Authors	No of cases	HPL level Low	Normal	High
1 Grumbach (1964)	1			+
Frantz (1965)	[illegible]	+		
3 Samaan (1966)	4	+		
4 Yen (1968)	1	+		
5 Saxena (1968)	7	+		
6 Goldstein (1971)	94	+	+	
7 Chough (1973)	9	+		
8 Sato (1973)	20	+		
9 Lim (1974)	40	+	1 case	1 case

Table II *Serum HPL and serum HCG in patients with intact hydatidiform mole*

No	Amenorrhoea (weeks)	Uterine size (weeks)	Serum HPL (µg/ml)	Serum HCG (IU/ml)	HPL (ng/ml) / HCG (IU/ml)	Sequelae
1	16	24	1 740	3?0	5 40	Chorio Ca
2	23	18	0 270	480	0 56	Chorio Ca
3	14	16	0 097	60	1 6?	Chorio Ca
4	12	18	0 090	480	0 19	Chorio Ca
5	35	22	0 180	60	3 00	
	36	22	0 170	?40	0 71	Chorio Ca
6	13	18	0 270	240	1 13	Chorio Ca
7	12	18	0 200	160	1 25	Chorio Ca
8	14	24	0 074	960	0 08	Chorio Ca
9	24	24	0 300	1 280	0 ?3	Chorio Ca
10	12	18	0 062	640	0 10	Benign
11	12	16	0 110	3?0	0 34	
	13	16	0 180	3 0	0 56	Benign
12	14	19	0 140	640	0 ??	Benign
13	31	?6	0 240	40	6 00	Benign
14	14	20	0 200	480	0 42	Benign
15	18	18	0 0_0	480	0 04	Benign
16	19	_0	0 130	480	0 27	Benign
17	9	12	0 030	1 ?60	0 02	Benign
18	12	16	0 013	1?0	0 11	
	13	17	0 036	320	0 11	Benign
	15	18	0 040	30	1 33	
19	16	24	0 130	480	0 ?7	Benign
0	19	24	0 1?0	3 0	0 38	Chorio Ca
21	17	24	0 010	160	0 06	Benign
22	12	24	0 350	1 280	0 ?7	Benign
	8	12	0 046	960	0 05	
23	13	16	0 080	480	0 17	Chorio Ca
	15	_0	0 180	960	0 19	
?4	11	18	0 047	480	0 10	
	12	18	0 060	3 0	0 19	Chorio Ca
	13	18	0 073	640	0 11	
25	18	14	0 010	_0	0 50	Chorio Ca
26	18	24	0 500	1 0	4 17	Benign
27	12	20	0 080	3 840	0 0?	Benign
28	14	20	0 100	480	0 ?1	Benign
?9	15	_0	0 110	480	0 ?3	Benign
30	18	28	0 230	300	0 77	Benign
31	12	22	0 080	1 280	0 06	Benign
32	19	24	0 010	1 9?0	0 01	Benign
33	24	18	0 180	10	18 00	Benign
	19	0	0 110	640	0 17	Benign
	17	_0	0 010	15	0 67	Benign
6	13	18	0 032	240	0 13	Benign
37	14	24	0 058	1 9?0	0 03	Benign
38	26	??	<0 005	160	0 03	Chorio Ca
39	16	24	0 100	1?0	0 80	Benign
40	15	?0	0 011	960	0 01	Benign

of our patients with hydatidiform mole present with abnormal uterine bleeding (18)

(*b*) All blood samples for assay were collected from cases just prior to the elective termination of the hydatidiform mole

(*c*) The final diagnosis of molar pregnancy was based on histologic examinations of the molar vesicles passed per vaginum or from material obtained at hysterectomy

Forty patients were available for this study single samples were obtained from each patient However 6 patients had more than one sample drawn during the course of investigations to confirm the diagnosis of molar pr nancy The final number of samples available were 48 gestational age of the hydatidiform mole ranged from 8 weeks Ten ml of venous blood was collected prior elective termination of the molar pregnancy The ser was separated within two hours of collection and store −20°C until ready for assay

Venous blood was similarly collected from 356 patie with normal pregnancy between 5–40 weeks Only o sample from each patient was taken to giv range of base line HPL in normal pregnan

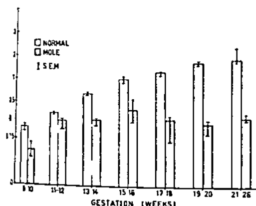


Fig 1 Mean±S E M Serum HPL in normal and molar pregnancy

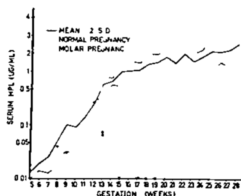


Fig 2 Serum HPL levels in molar pregnancy

f selection of patients were as laid out in a previous study by the same authors (9) The number of assays per gestational week ranged from 4–70

Serum HCG was measured by the hemagglutination-inhibition method of Wide (19) as modified by Teoh (17) Serum HPL was measured by radioimmunoassay method as previously described by Lim et al (9) This is a highly specific and rapid method for measuring serum HPL and a modification of the method of Letchworth et al (8) The HPL standard was from Amersham radiochemical centre UK The sensitivity of the assay was such that values of less than 0 005 μg/ml cannot be detected.

RESULTS

Table II illustrates the endocrine and clinical profile of the 40 cases Table III shows the mean± S E M HPL values in patients with intact hydatidiform mole when compared to the levels found in normal pregnancies of corresponding gestational age The results indicate that HPL levels were significantly lower in cases of intact molar pregnancy than in patients with normal pregnancies of similar gestation This is also depicted as a histogram in Fig 1 The HPL values in intact molar pregnancies ranged from 2–30 times lower than normal pregnancies of the corresponding period of gestation However normal and occasional higher than normal values were observed for the corresponding period of amenorrhoea (Table IV)

Fig 2 shows the serum HPL values for the intact hydatidiform moles superimposed on the sectional

Table III *Serum HPL and HCG levels in normal and molar pregnancies*

Type of pregnancy	Gestation (weeks)	No of cases	Mean HCG (IU/ml)	HPL (μg/ml) Range	Mean±S E M	Difference
Normal	8–10	24	100	0 038–0 147	0 080±0 007	$p<0\ 0005$
Mole		2	1 1.0	0 030–0 046	0 038±0 008	highly significant
Normal	11–12	18	125	0 151–0 420	0 .86±0 019	$p<0\ 0005$
Mole		10	892	0 013–0 350	0 109±0 031	highly significant
Normal	13–14	8	95	0 540–0 750	0 686±0 027	$p<0\ 0005$
Mole		12	565	0 032–0 770	0 115±0 0.2	highly significant
Normal	15–16	13	60	0 700–1 4 0	1 0.0±0 065	$p<0\ 0005$
Mole		7	478	0 011–1 740	0 330±0 236	highly significant
Normal	17–18	17	45	0 740–2 000	1 .43±0 072	$p<0\ 0005$
Mole		6	182	0 010–0 500	0 130±0 082	highly significant
Normal	19–.0	18	40	1 170–2 340	1 674±0 069	$p<0\ 0005$
Mole		4	840	0 010–0 130	0 092±0 027	highly significant
Normal	21– 6	69	.5	1 0 0–3 5 0	1 876±0 056	$p<0.0005$
Mole		4	483	0 005–0 300	0 189±0 067	ant

Table IV *Range of serum HPL levels in intact molar pregnancies*

Values	Range	No of cases	Case number
(A) Very low	31–100 times lower than normal	9	Cases 15 17 18 21 25 3? 35 38 40
(B) Low	2–30 times lower than normal	29	The remaining 29 cases excluding (A) (C) (D)
(C) Normal	–	1	Case 22
(D) High	–	1	Case 1

normal HPL curve based on 356 normal pregnancies

Serum HPL and uterine size There was no significant correlation between HPL values and uterine size (coefficient of correlation $r=+0.3$) This is represented in Fig 3

Serum HPL and serum HCG No significant correlation exists between serum HPL and serum HCG for any given case of hydatidiform mole (coefficient of correlation $r=0.00017$) This is represented in Fig 4

Ratio of HPL to HCG (ng/ml I U /ml) In normal pregnancy good correlation is seen between this ratio and gestation period The base line HPL and HCG values were obtained from local series of Lim et al (9) Low ratio values were seen in all cases of hydatidiform mole This is depicted in Fig 5

Outcome of molar pregnancy

An attempt to predict the final outcome of the molar pregnancy was attempted This was done by expressing as an endocrine ratio of HPL/HCG for given case of molar pregnancy No correlation ship was found This is to be expected since there is no significant correlation between serum HCG and serum HPL for any given case of hydatidiform mole Fig 6 illustrates this point

DISCUSSION

HPL is produced by the prophoblast both in vivo and in vitro (10 11) Studies with tissue culture indicate that the production of HCG is the most primitive property of the trophoblast in the undifferentiated stem cell state HPL is produced primarily in the differentiated trophoblast it is only present in small amounts in the undifferentiated stem cell (10)

Original work by Saxena et al (13) show that HPL levels in molar pregnancies were always significantly low and that there was no overlap with normal values Josimovich (7) suggested that molar pregnancy could be diagnosed on the basis of low serum HPL The present authors do not wholly agree with this Though the majority of values were

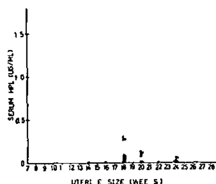


Fig 3 Relationship between serum HPL and uterine size in intact molar pregnancy

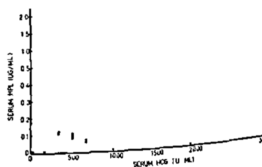


Fig 4 Relationship between serum HPL and serum HCG in intact molar pregnancies

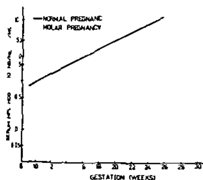


Fig 5 Ratio of serum HPL/HCG in normal and molar pregnancies

low values were sometimes within the normal preg nancy range before the mole aborted and occasion ally fairly high values were present as shown in study Previous low values as reported may be obtained from patients who had already aborted ar vesicles An aborted but unevacuated pregnancy is quite a different clinical entity in an intact molar pregnancy It may be that w levels of HPL as hitherto reported may be due to the passage of molar vesicles with decrease tro- astic mass Good correlation between serum L and trophoblastic mass have been reported by elenkow (15) and Seppala et al (16) In vitro cell ulture experiments of HPL content in molar tissue Sato (12) showed that HPL content tend to be er in the third month of molar pregnancy when ared with similar gestation of normal preg ancy However no difference was observed be en the two in the fourth month of pregnancy

Abnormal uterine bleeding was the presenting in all the forty cases under study It is poss e that repeated recurrent bleeding with resultant uction of trophoblastic tissue may lead to duced levels of circulating HPL (3 21) Thus the and severity of bleeding per vaginum may d be reflected in the lower levels of HPL in cases f hydatidiform mole

We do not agree that the level of serum HPL in ydatidiform mole is a reflection of the length of (4) Table III show that the highest mean L level in hydatidiform mole occurred in the 5–16 gestational week (0 33 μg/ml) While mean in later gestational weeks were much lower (17–18 weeks=0 13 μg/ml 19–20 weeks=0 092 μg/ml 21–26 weeks=0 189 μg/ml)

Goldstein (4) proposed that the level of HPL is inversely proportional to the degree of malig nancy of the hydatidiform mole This was not found to be so in the present study Neither the level of HPL per se nor the ratio of HPL/HCG was any indicator of the final outcome of the molar pregnancy The histologic grouping employed by Goldstein according to the criteria of Hertig & Shel don (6) have been noted to be unreliable by Tow (18)

In conclusion serum HPL in intact hydatidiform mole was not found to be invariably low as pre viously reported Values ranging from very low to *those higher than the corresponding gestational age* of normal pregnancy were found Serum HPL level per se is of some clinical use as an endocrine index in the diagnosis of hydatidiform mole But when combined with HCG a low HPL/HCG ratio for the corresponding period of amenorrhoea is a useful index in the diagnosis of hydatidiform mole

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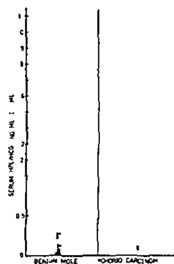


Fig 6 Ratio of HPL/HCG and outcome of molar preg nancy

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CHANGES IN AMNIOTIC FLUID PHOSPHOLIPIDS ON TREATMENT WITH GLUCOCORTICOIDS TO PREVENT RESPIRATORY DISTRESS SYNDROME

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Amniotic fluid was obtained by transabdominal sis in 51 women in the 29th–36th week of ncy The lecithin/sphingomyelin ratio was de ermined In 28 patients the ratio was <2 2 Beta ethasone was given for three days to 14 of them the rest as controls On the fourth day a second amnio was performed on all patients The leci n/sphingomyelin ratio rose to a value >2 2 in 4 of the ts in the betamethasone treated group and in one of The percentage of palmitic acid in the lecithin eased concomitantly with increasing lecithin/sphingo- These results suggest that glucocorticoid ation of fetal pulmonary maturation may be in the amniotic fluid as changes in its phospholipid ion The lecithin/sphingomyelin ratio was found be >2 2 in 23 patients at the first amniocentesis In such treatment with glucocorticoids can be avoided

piratory distress syndrome (RDS)—character by expiratory grunting tachypnea persisting ter the first hour of life marked and persistent subcostal and intercostal recession during spiration cyanosis and characteristic radiographic ngs of diffuse reticulogranular mottling in the fields and an air bronchogram (17)—is as with defiency of pulmonary surfactant (2) mature infants are most susceptible to develop of RDS but the condition has also been served in infants born at term Dipalmitoyllecithin an important component of the pulmonary actant (19) It is secreted into the alveoli During piratory movements it reaches the amniotic d (3) Analysis of amniotic fluid phospholipids t possible to estimate pulmonary maturity he risk of the new born developing RDS (10 16) this is of limited practical value without appropriate therapeutic means of accelerating the maturation of the fetal lungs

In recent years many investigators have tried to find pharmacological means to accelerate pulmonary maturity For this purpose several drugs such as heroin (15 31) thyroxin (26 33) isoxsuprine (18 34) methylxanthine (23) ritodrin (4) bromhexine metabolite VIII (8 24) and oestrogen (30) have been suggested The effect of glucocorticoids has been most extensively studied Thus accelerated lung maturation with enchancement of surfactant production and secretion has been demonstrated in animal experiments (9 20 21 25) in tissue culture studies (11 13 28 29 32) and in clinical studies (6 7 14 22)

The present investigation is a controlled clinical trial to evaluate antepartum glucocorticoid treatment for preventing RDS as judged from changes in the composition of amniotic fluid phospholipids

MATERIAL AND METHODS

Amniotic fluid was obtained by transabdominal amniocentesis in 51 women in the 29th–36th week of pregnancy All were in hospital because of complications in the form of threatened premature labour ($n=28$) suspected placental insufficiency ($n=6$) Rh immunization ($n=2$) suspected abruptio placentae ($n=$ litus ($n=1$) malignant melanoma ($n=$ lymphoma ($n=2$) and increased concent fibrinogen fibrin degradation products (FD amniotic fluid lecithin/sphingomyelin ratio on the day of amniocentesis Where the myelin ratio was <2 2 every second pat fast acting betamethasone disodium pho slow acting betamethasone acetate (C

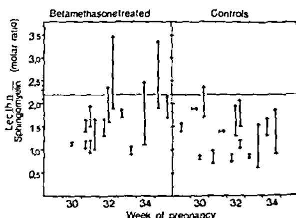


Fig 1 Individual lecithin/sphingomyelin ratios in amniotic fluid obtained by amniocentesis with 4 days interval The base of the arrow indicates the first value and the head the second

Schering corp) i m daily for 3 days On the fourth day all patients underwent a second amniocentesis with subsequent analysis of the phospholipids The analytical results were not disclosed to the obstetricians who had to treat the patients

Analytical

The amniotic fluid samples were centrifuged at 1000 *g* for 15 min and the supernatants were decanted The lipids of the supernatants were extracted with chloroform–methanol 2 1 (v/v) and the phospholipids were separated by thin layer chromatography (27) The lecithin and sphingomyelin fractions were isolated quantitatively (1) and their P-content was determined spectrophotometrically The fatty acid composition of the lecithin fraction was determined by gas–liquid chromatography

RESULTS

e lecithin/sphingomyelin ratios of the amniotic fluid samples obtained at the first amniocentesis were <2 2 in 28 patients Celestona Bifas® was giv to 14 of them In the amniotic fluid obtained at second amniocentesis the lecithin/sphingomyel ratio exceeded the value of 2 2 in 4 of the patients the betamethasone treated group and in one of controls (Fig 1) The percentage of palmitic acid the lecithin increased concomitantly with increas lecithin/sphingomyelin ratio (Table I) Table II gi individual analytical and clinical data of the be methasone treated patients and Table III that of controls No infant developed RDS The 23 patie that had an initial lecithin/sphingomyelin ratio > were in the 31st–36th week of pregnancy The co plications of these pregnancies were imminent p mature labour (*n*=12) Rh immunization (*n*=5) t aemia (*n*=2) suspected placental insufficie (*n*=1) suspected abruptio placentae (*n*=1) malignant lymphoma (*n*=2) No infant develop RDS

DISCUSSION

In a clinical trial Liggins et al (22) demonstrate significantly lower incidence of RDS in premat infants delivered after betamethasone treatment the mother In a few cases the lecithin/sphing myelin ratio of amniotic fluid samples obtained fore treatment and after treatment was determ but no figures were given The trial was repeated Fargier et al (11) who confirmed the results Liggins et al (22) Spellacy et al (30) treated patie in the 28th–32nd week of pregnancy with d methasone for two weeks The mean differen e tween the lecithin/sphingomyelin ratio before tre ment and after treatment was higher in these p than in a control group Caspi et al (6) reported case of premature rupture of the membranes

Table I *Fatty acid composition of amniotic fluid lecithin in five cases with lecithin/sphingomyelin r ≥2 2 after treatment with betamethasone*

The fatty acids are designated by (number of carbon atoms) (number of double bonds)

	Pre treatment						Post treatment					
	Fatty acid (mol percent)					Lec /sph (molar ratio)	Fatty acid (mol percent)					Lec /sph (molar ratio)
	14 0	16 0	16 1	18 0	18 1		14 0	16 0	16 1	18 0	18 1	
1	1 9	71 8	2 2	11 0	13 1	1 9	2 4	86 4	0 7	8 9	1 5	3 4
2	1 6	67 8	1 5	15 4	13 7	1 1	1 2	85 7	trace	9 3	3 8	2 5
3	1 3	72 0	7 7	10 6	8 4	1 6	0 5	81 5	1 6	9 4	7 1	[illegible]
4	3 6	70 5	4 4	13 3	8 2	1 6	2 8	76 4	1 1	11 9	7 8	[illegible] 4
5	2 1	67 6	2 0	16 7	11 8	1 9	3 2	84 2	1 1	9 9	1 6	3 5

Table II *Individual data of betamethasone treated patients*

Case no	Complication of pregnancy	Gest age (weeks)	Lec /sph (molar ratio) Amn c 1	Amn c 2	Gest age at delivery (weeks)	Birth weight (g)
1	Susp plac insuff	30	1 1	1 2	35	1 540
2	Impending premature labour	31	1 2	1 0	40	3 300
3	Impending premature labour	31	1 4	1 7	36	2 190
4	Susp plac insuff	31	1 2	0 9	34	1 2?0
5	Susp plac insuff	31	1 5	2 0	36	230
6	Impending premature labour	31	1 0	1 7	37	2 800
7	Impending premature labour	32	1 3	1 7	40	2 630
8	Impending premature labour	32	1 6	? 4	37	2 820
9	Impending premature labour	32	1 9	3 5	40(?)	2 300
10	Impending premature labour	33	1 7	1 9	38	2 830
11	Rh immunization	33	0 9	1 1	37	2 500
	Impending premature labour	34	1 1	? 5	40	3 850
3	Susp plac insuff	35	1 6	? ?	38	2 450
4	Impending premature labour	35	1 9	3 4	36	1 940

The lecithin/sphingomyelin ratio remained un changed for 8 days but rose sharply after treatment th dexamethasone for three days Recently Caspi al (7) reported a rise in amniotic fluid ecithin/sphingomyelin ratios to values over 2 after nethasone administration Dexamethasone owever was given in various dosages and dministered in different ways moreover the inter al between pre and posttreatment amniotic fluid amples varied from case to case and they did not rt any controls

In the present investigation the amniotic fluid ples were obtained identically in both the beta nasone treated group and in the controls Be thasone was administrated i m in the same dosage to all treated patients and the second sample of amniotic fluid was obtained after the same inter val

The results thus show that the amniotic fluid lecithin/sphingomyelin ratio exceeded the value of 2 2 in 4 of the betamethasone treated patients and in one of the controls

The value of 2 2 was chosen on the basis of an earlier prospective study (10) using the same analyti cal technique In that study 9 infants developed RDS In 7 of these cases the lecithin/sphingomyelin ratio in amniotic fluid obtained 0 5–5 hours before delivery was <2 0 The other 2 had a value of 2 2 The lowest value hitherto observed with our ana lytical method among newborns not developing RDS

Table III *Individual data of controls*

Case no	Complication of pregnancy	Gest age (weeks)	Lec /sph (molar ratio) Amn c 1	Amn c 2	Gest age at delivery (weeks)	Birth weight (g)
1	Rh immunization	?9	1 4	1 6	37	2 7?0
	Rh immunization	30	1 9	1 9	37	2 760
3	Impending premature labour	30	0 8	0 9	39	3 860
4	Impending premature labour	30	1 7	2 4	36	2 140
5	Impending premature labour	31	0 7	1 0	42	4 7 0
6	Impending premature labour	31	1 4	1 4	34	2 020
7	Diabetes mellitus	3?	0 9	0 7	39	2 170
8	Susp plac insuff	32	1 3	2 0	35	1 930
9	Increased conc of serum FDP	32	1 2	1 0	40	2 400
0	Impending premature labour	32	1 5	2 1	38	2 960
11	Impending premature labour	33	0 9	0 8	38	2 360
12	Susp abrup plac	33	0 6	1 6	37	2 610
13	Malignant melanoma	34	1 3	1 7	36	2 210
4	Impending premature labour	34	0 9	1 9	4 (?)	3 910

6?865

is 2 0 Probably a borderline group exists with a lecithin/sphingomyelin ratio between 2 0 and 2 5

The concomitant increase in the percentage of palmitic acid in the lecithin indicates that be tamethasone enhanced the synthesis and release of dipalmitoyllecithin Recently we found evidence both *in vitro* (12 13) and *in vivo* (11) of accelerated production of dipalmitoyllecithin in human fetal lung tissue after administration of glucocorticoids The effects were observed as early as the second trimester of pregnancy and within 2 days of treatment This agrees with observations by Liggins et al (22) that premature infants delivered 48 hours or later after betamethasone treatment of the mother had a lower incidence of RDS

It is notable that betamethasone failed to increase the lecithin/sphingomyelin ratio to a value over 2 2 in several cases This could be because betamethasone stimulated the synthesis of dipalmitoyllecithin in the lung tissue but the substance did not reach the amniotic fluid

In high risk pregnancies the excretion of urinary estriol is routinely determined The present study noted a tendency to reduction of this excretion after betamethasone administration which agrees with previous observations (5) This side effect prevents the use of a helpful parameter for assessing placental function

This study further demonstrates the value of determining the amniotic fluid lecithin/sphingomyelin ratio in high risk pregnancies where premature delivery is considered or imminent Of the 51 patients 23 had a lecithin/sphingomyelin ratio >2 2 already at the first amniocentesis In such cases treatment with glucocorticoids with uncertain side effects can be avoided The results also suggest that glucocorticoid induced acceleration of fetal pulmonary maturation may be reflected in the amniotic fluid as changes in its phospholipid composition

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THE VALUE OF AMNIOTIC FLUID LECITHIN/SPHINGOMYELIN DETERMINATION IN PREDICTION OF HYALINE MEMBRANE DISEASE

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stract 46 samples of amniotic fluid were obtained m 45 women with normal or complicated pregnancy or at parturition The lecithin/sphingomyelin (L/S) tio was determined and retrospectively correlated with n cal course of the neonate Ten neonates de loped hyaline membrane di ease (HMD) The highest atio in this group was 1 8 Cesarean section was not sociated with HMD if L/S ratio indicated pulmonary (L/S>) With the exception of children born by men with toxemia or chronic hypertensive disease here no case of HMD appeared among nine infants with birth weights <2000 g developed HMD in out 50% (6/11 cases) The results show that the L/S io correlates well to the pulmonary maturity of the nate Determination of L/S ratio is therefore of great portance in cases of high risk pregnancy or doubtful tational age prior to induction or Cesarean section

ory distress syndrome or hyaline mem disease (HMD) is a major cause of neo- tal death (3) and antenatal prediction of fetal pul n ary maturity is therefore necessary when in on er elective Cesarean section before term is dered

It has been shown by Avery & Mead (4) and (1) that there is possibly a relationship be een a deficiency of surface active material y lecithin in the lung and later development of aline membrane disease in the fetus In 1969 elson (35) suggested that antepartum analysis of ic fluid phospholipids might be useful as a d to evaluate the amount of surface active mater in the fetal lung Gluck et al (22) utilized the ithin/sphingomyelin concentration ratio (L/S) to redict the amount of surface active material in the tal lung—the pulmonary maturity According to luck (23) the factors causing HMD seems to be an inability to meet the demands of post natal respiratory adjustment by synthesis of sufficient amounts of surface active pulmonary lecithin

In earlier investigations (15 32) we showed that L/S ratios correlated closely with gestational age in normal and complicated pregnancy and that this could be used to determine gestational age The purpose of the present study was to determine the reliability of the L/S ratio in predicting the postnatal occurrence of HMD The incidence of HMD in relation to route of delivery Apgar score birth weight and complications of pregnancy such as diabetes iso immunization and toxemia were also investigated

MATERIALS AND METHODS

246 samples of amniotic fluid obtained from 245 pregnancies terminating in the birth of 246 live infants delivered within 3 days of sampling were analysed and L/S ratio and creatinine concentration were determined 16 of the pregnancies were normal and 84 cases were complicated (Tables I and II) Serial analy is of L/S ratio and creatinine were performed in 6 of the pregnancies The indication for abdominal amniocente is was Rh immunization uncertain gestational age and assessment of possible presence of meconium in high risk pregnancy In uncomplicated cases amniotic fluid was collected mostly via amnioscope at delivery Specimens containing blood or meconium were not included since these substances may interfere with the estimation of L/S-ratio (15)

Seven additional samples were obtained from pregnancies resulting in deliveries of dead children

Assessment f the pregnancies

Toxemia Diagnosis and classification of toxemia of pregnancy was made according to recommendations of the U S Committee on Maternal Welfare (25) To this group

Table I *Distribution of material in relation to respiratory state of infant*

0=no respiratory problem HMD=hyaline membrane disease RD=respiratory distress due to other causes N=246

	0	HMD	RD
Normal	151	6	5
Toxemia	34	1	2
Iso-immunization	32	2	1
Diabetes	11	1	0

In two cases hemorrhage occurred during labor possibly due to placental abruption

Table III *Respiratory state of infant in relation to different intervals of L/S ratio*

0=no respiratory problem HMD=hyaline membrane disease RD=respiratory distress due to other causes

Respiratory states of infant	L/S ratio <1 5	1 5–1 74	1 75–?0	> 0
0	2	3	11	?1?
HMD	5	3	?	0
RD	1	?	?	3
Incidence of respiratory problem	6/8	5/8	4/15	3/?15
Incidence of HMD	5/8	3/8	2/15	0/ 15

belong (*a*) mild toxemia (*b*) severe toxemia (*c*) chronic hypertensive disease

Diabetes mellitus The White classification was used for the patients with diabetes (45)

Iso-immunization Cases were grouped according to Jonasson (29) where group I represents the children with cord hemoglobin ≥12 1 g/100 ml and requiring at most one exchange transfusion group II with cord hemoglobin within the range 8 1–12 0 g/100 ml or requiring ?–3 exchange transfusions and group III with cord hemoglobin 8 0 or lower or requiring more than 3 exchange transfusions

Assessment of the new born

Hyaline membrane disease (HMD) HMD was defined according to Hutchison s criteria (28) difficulty with respiration apparent within 4 hours of delivery persisting for at least 48 hours tachypnea sternal or intercostal recession cyanosis and expiratory grunting and characteristic radiographic changes—diffuse reticulogranular mottling of the lung fields Blood gas studies from umbilical cord demonstrated hypoxemia and acidosis

Respiratory distress (RD) RD was considered if respiratory difficulties were present but failed to fulfil the criteria for the diagnosis of HMD In most cases other causes could be found for the RD

The L/S ratio in amniotic fluid was determined by modification of Gluck s technique (?) as previously described (15) Amniotic fluid was centrifuged at 000×g fo 10 min and the supernatant filtered through filter paper To 5 ml of the filtrate 12 5 ml methanol and after shaking 12 5 ml chloroform were added The homogenous ph was allowed to stand for about 30 min at room temperature and then 6 ?5 ml 0 9 NaCl was added and the mixtu shaken (?) After phase separation the lower chlorofo phase containing the lipids was recovered and taken dryness under a stream of nitrogen The lipids were d solved in 100 microliters of chloroform and 10– 0 micro ters applied to 0 25 mm TLC plates coated with silica H The plates were developed with chloroform/meth nol/acetic acid/water 25/15/4/1 (by vol) the spots v ualized by charring with H_2SO_4 and L/S ratio determin as previously described (15)

able II *Distribution of material and birthweight (g) of infant and its respiratory state*

no respiratory symptoms HMD=hyaline membrane disease RD=respiratory distress due to causes other th MD N=246 Diagnostic definitions are given in the text

	Weight <1 500			1 500–? 000			2 000–? 500			>2 500		
	0	HMD	RD	0	HMD	RD	0	HMD	RD	0	HMD	F
Normal		1		1	2	1	5	1	1	145	2	1
Diabetes ABC					1					7		
Diabetes DEF				1			1			?		
Iso-immunization												
Group I					2					?0		1
Group II							1			8		
Group III							3					
Toxemia mild						1	?			14		
Toxemia severe	1		1	4			2			3		
Chronic hypertensive disease	1			1			1	1		5		
Placental abruption			1			1						

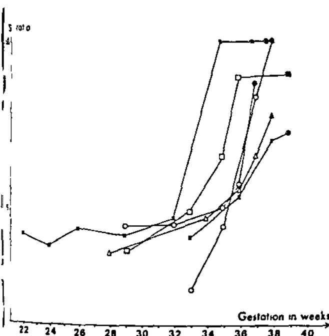


Fig 1 L/S ratio in amniotic fluid versus gestation in weeks serially determined in 6 patients with normal and complicated pregnancy All the infants healthy × normal pregnancy O iso-immunization Δ toxemia □ diabetes At delivery ⊗ ● ▲ ■

RESULTS

ble I lists the distribution of material and the dence of HMD and RD in each group No ificant difference was found between the Table II shows the classification of material subgroups with regard to birth weight and re ratory status of the infant With the exception of en born by women with toxemia or chronic pertensive disease where no case of HMD ap among nine infants about 50% (6/11) of the en with birth weight <2000 g in the other developed HMD Route of delivery and the respiratory status is presented in Table IV In this respect there was no appreciable difference be tween cases of induced and spontaneous labor Three children delivered by Cesarean section de veloped HMD but the gestational age was in two cases incorrectly estimated to be near term (Table VI) Table V shows the incidence of HMD and RD correlated to Apgar scores Low Apgar scores were found in four cases associated with HMD i e pos sibly an increased rate in asphyxia

Table III shows the respiratory status of infants related to L/S ratio A L/S ratio ≥2 suggests pul

IV *Number of newborn infants without re ratory problems (0) or developing hyaline ane disease (HMD) respiratory distress due other causes (RD) or transient asphyxia post um in relation to mode of delivery*

piratory status fant	Mode of delivery: Spontaneous	Induction with oxytocin	Cesarean section
	139	58	19
	6	1	3
	6	1	1
onatal asphyxia	6	4	-

One infant died

Table V *Number of cases with hyaline membrane disease (HMD) and respiratory distress due to other causes (RD) related to 5 minute Apgar scores and L/S ratio*

	L/S ratio <1.5	1.5–1.74	1.75–2.0	>2.0
Apgar ≥7				
HMD	4	1	1	0
RD	1	1	1	3
Apgar <7				
HMD	1	-	1	0
RD	0	1	1	0

One infant died

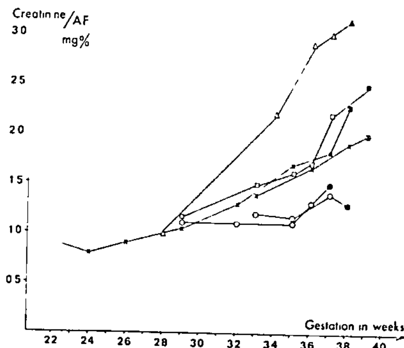


Fig 2 Creatinine concentration (mg%) in amniotic fluid versus gestation in weeks serially determined in 6 patients with normal and complicated pregnancy All the infants healthy × normal pregnancy ○ iso immunization △ toxemia □ diabetes At delivery ⊙ ● ▲

Table VI *Pregnancy and delivery data on patients that delivered infants with subsequent hyaline membrane disease*

Case no	Gestational age (weeks)	L/S ratio	Creatinine/AF (mg%)	Maternal complication	Labor	Birth weight (g)	Sex	Remarks
251	About 35	1 11	1 1	Iso-immunization	Induction	2 000	♂	HMD on X ray Severe recovered
665	34–38	1 18	1 5	Diabetes (C) and hepatosis	Failed induction and cesarean section	1 8 0	♀	HMD on X ray Moderate recovered Probably premature
08	36	1 80	1 5	Intrauterine death×2	Elective cesarean section	2 760	♀	HMD on X ray Mild recovered
250	33	1 67	1 3	–	Spontaneous	2 030	♂	HMD on X ray Moderate recovered
552	About 40	1 30	1 5	–	Spontaneous	3 60	♀	HMD on X ray Moderate recovered
811	32	1 54	1 1	Premature rupture of membranes 24 hours	Spontaneous	1 450	♂	HMD on X ray and at post mortem examination Died after 7 hours
693	34 or 38	1 42	2 5	Chronic pyelonephritis and hypertension	Elective cesarean section	2 160	♂	HMD on X ray Probably premature and not small for date Recovered
178	31	1 82	1 7	–	Spontaneous	1 690	♀	HMD on X ray Moderate recovered
576	About 30	1 41	1 1	Iso immunization	Spontaneous	1 540	♂	HMD at postmortem examination Died after 7 hours
202	33	1 54	1 6	Multiple pregnancy	Spontaneous	1 960	♀	HMD on X ray Moderate recovered Twin no II
01	33	2 14	1 5		Spontaneous	2 100	♂	No respiration problems Twin no I

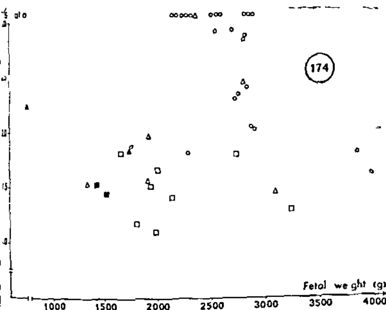


Fig 3 Occurrence of respiratory distress in relation to L/S ratio and birth weight $N=246$
174 infants without respiratory problems O no respiratory problems □ HMD recovered ■ HMD died Δ RD recovered (causes other than HMD) ▲ RD died (causes other than HMD)

…monary maturity In the group with L/S ratio <1 75 …0% developed HMD Fig 3 shows the occurrence of respiratory problems in relation to L/S ratio and birth weight With a L/S ratio >1 82 no cases of HMD appeared irrespective of birth weight RD seemed to be correlated neither to L/S ratio nor birth weight Serial determination of L/S ratio and creatinine in 6 patients is shown in Figs 1 and 2 It is notable that the toxemia patient had a high creatinine value already in the 34th week while the cor

Table VII *Pregnancy and delivery data on patients that delivered infants with respiratory distress (RD) not classified as HMD*

Case no	Gestational age (weeks)	L/S ratio	Creatinine/AF (mg%)	Maternal complication	Labor	Birth weight (g)	Sex	Remarks
113	36	5 58	1 9	–	Spontaneous	2 4 0	♀	Transient tachypnea X ray normal
10	37	1 45	1 6	–	Spontaneous	3 110	♀	Tachypnea and cyanosis from birth Ductus arteriosis Botalli
171	38	45	1 4	Iso-immunization	Induction	2 850	♂	Exchange transfusion×2 X ray Pneumonia?
144	35	1 97	1 7	Toxemia	Spontaneous	1 960	♂	Intrauterine asphyxia X ray normal Recovered after 1 day
137	33	1 57	1 5	–	Spontaneous	1 940	♂	Transient tachypnea No X ray
561	About 33	1 54	1 9	Toxemia, placental insufficiency	Cesarean section	1 360	♂	Mild transient respiratory problems X ray normal
774	33	1 84	1 4	Placental abruption	Spontaneous	1 770	♂	Died 10 min post partum Cerebral hemorrhage at postmortem examination
57	About 7	4	–	Placental abruption	Spontaneous	750	♀	Died after 2 days Intracranial hemorrhage Lungs normal at autopsy

Table VIII *Data on patients and infants in cases with oligo or polyhydramnios*

Case no	Gestational age (weeks)	L/S ratio	Creatinine/AF (mg%)	Maternal complication	Labor	Birth weight (g)	Sex	Remarks
253	About 30	2 70	1 4	Toxemia placental insufficiency	Induction	970	♀	Intrauterine death 3 weeks after amniocentesis Dysmaturity Oligohydramnios
607	33	1 77	1 6	Toxemia placental insufficiency	Cesarean section	9 0	♂	No problems of respiration Delivery 3 days after amniocentesis Oligohydramnios slight contamination of meconium
593	37	- 16	1 5	Duplex	Spontaneous	2 070	♂	Died intrauterine Polyhydramnios The other twin healthy
53	41	1 61	–	–	Spontaneous	4 380		Healthy ? l amniotic fluid
723	39	3 34	–	–	Induction	3 500		Died in utero 1 day after amniografi Polyhydramnios 0 anomalies
550	34	1 40	1 0	–	Spontaneous	1 150		Died intrauterine Polyhydramnios 3 5 l Multiple anomalies anencephalic hypoplasia of suprarenal glands
757	41	1 09	1 9	–	Spontaneous	3 160		Died intrapartum Polyhydramnios 3 l Multiple anomalies porencephali and cranial synostosis
814	30	1 68	0 9	–	Spontaneous	1 350		Died intrapartum Polyhydramnios 7 l Multiple anomalies of cor kidney and micrognati
254	41	1 53	–	–	Induction	About ? 000		Died in utero Polyhydramnios Anencephalic

responding L/S ratio still was low The spread of L/S ratio in the 35th week was large

Individual data from ten cases of HMD are collected in Table VI Case 693 developed HMD the atinine value in amniotic fluid was high (Cr/s 1 0) L/S ratio was low 1 42 The birth weights were n 50% ≥2000 g No sex difference was found The highest L/S ratio in these ten cases was 1 82 The twins (no 202 and no 201) had L/S ratios predictive of their individual clinical courses

Table VII shows individual data from eight cases developing RD Low L/S ratios were found in case 210 and case 561 but the diagnosis HMD could not be verified It is of interest that the very premature case 252 had a high L/S ratio and no signs of HMD at autopsy

Data from two complicated cases of severe placental insufficiency is shown in Table VIII Seven cases of polyhydramnios are also presented and the majority had multiple anomalies including malformations of the central nervous system The L/S ratios were very low in relation to gestational a compared to other pregnancies (32)

DISCUSSION

The clinical value of measuring phospholipids i amniotic fluid as an index of the production of pulmonary surfactant and thereby lung maturity wa first studied by Gluck (22) and his conclusion tha HMD is unusual when the L/S ratio >? was subsequently corroborated by many others (9 1? 18 ?7 30 39) The absolute values for the L/S ratio above which HMD is unusual varies between different investigators probably mostly for methodological reasons With the exception of Schulman (41) most investigators find L/S ratios of 1 5-? to be values above which HMD is uncommon This is in good agreement with our results (Table III) Roux et al (37) on the other hand postulated that the L/S ratio indicates fetal age but not specifically lung

maturity Data from specific studies with radio active precursors (36) in amniotic fluid and changes in amniotic phospholipids following tracheal ligation (7 0) have however established that there is transport of surfactant from fetal lung to amniotic fluid.

Various ways to determine phospholipid concentration in amniotic fluid have been used (8 22, 6) The technique employed in this investigation—acetone precipitation omitted (15)—gives the total lecithin fractions and does not alter the L/S ratio compared with other methods (4 8) Another method of estimating the amount of surfactant is the determination of lecithin concentration (6) but excessive variations in the volume of amniotic fluid may produce misleading results which may be of crucial importance in high risk pregnancies (6 13) Clements et al (11) have proposed a rapid shake test to be valuable as a screening procedure for determining fetal lung maturity (40 44)

Not a single case of HMD developed among the nine low birthweight toxemia infants in contrast to other infants <2000 g (Tables II and VI) The difference might partly be due to the fact that infants in the former group probably were small for dates in some cases and partly that lung maturity seems to be more rapid in cases with toxemia maternal hypertension (21 32) small for dates or placental abruption (24) independent of gestational age or birth weight Toxemia and placental insufficiency might be stress stimuli which raise the fetal plasma corticosteroid levels and cortisol is presumed to be an important physiological inducer of the pathways responsible for the synthesis of surface active material in the lung (31) This would be in agreement with the observations by Murphy (33) who found cortisol levels in umbilical cord blood at delivery to be lower in infants with HMD This finding was however not confirmed in other investigations (5 16) It has recently been suggested that the level of total amniotic fluid cortisol may reflect the initiation of fetal lung maturation (14)

Anencephalic fetuses seem to have low amounts of surface active material in the lung (35 Table VIII) According to Naeye (34) who found anencephalic neonates with hypoplasia of the adrenal cortex this may be an expression of deficient adrenal function Reduced adrenal weight in neonates dying from HMD was also reported (34) but not by

HMD is said to occur predominantly in infants delivered by Cesarean section (3 43) and among infants of diabetic mothers (3) This is however refuted by others (12 17) Cesarean section is often associated with prematurity but a weight >2500 g does not necessarily exclude the development of HMD (Table VI) The data in this report (Tables I IV VI) suggest that delivery by Cesarean section did not increase the incidence of HMD when the fetal lung was mature (L/S >2) prior to operation

The incidence of HMD associated with L/S ratios <2 0 was 32% (Table III) This is lower than reported by Gluck & Kulovich (21) who found 90% HMD if L/S ratio <2 0 but similar to Spellacy & Buhi (42) and Kalbach (30) 33 and 48% respectively Differences may be a result of different methodoloy or the length of time between amniocentesis and delivery

Low Apgar scores have been suggested to be associated with a higher morbidity from HMD (12) No conclusions can be drawn from our material supporting this because the number of cases is so small but possibly a certain trend in the same direction is present (Table V) According to Gluck the methyl transferase reaction in which palmitoyl myristoyl lecithin—a component of the surface active material in the lung—is synthesized is very sensitive to acidosis (19) This can however hardly be the reason for the proposed association between low Apgar score and HMD (12) as neonates delivered from pregnancies with chronic intrauterine asphyxia tend to develop HMD less frequently compared with normal or other complicated pregnancies (Table II and VIII)

The L/S ratio had a high degree of reliability in predicting fetal lung maturity A ratio of >2 0 indicated a mature lung and a ratio <1 75 indicated that the risk of development of HMD was very high Prior to elective Cesarean section or induction it is thus of great importance to determine the L/S ratio if gestational age is uncertain as HMD might appear in spite of a high value of creatinine in amniotic fluid (Table VI Figs 1 and 2)

In high risk pregnancy the L/S ratio gives useful information to the obstetrician in the decision of the timing of delivery There is evidence that a damage to the central nervous system can be demonstrated in later life in many children with prolonged exposure to a poor intrauterine environment (46) Thus in certain very high risk pregnancies delivery usually by Cesarean section should be considered

as soon as the L/S ratio predicts lung maturity (Table VIII) to avoid increased risk of cerebral sequelae or intrauterine death

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A COMPARATIVE STUDY OF PATIENTS WITH CANCER OF THE OVARY WHO HAVE SURVIVED MORE OR LESS THAN 10 YEARS

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Abstract With the purpose of elucidating the characteristics in patients with cancer of the ovary who have survived 10 years compared with patients who have not survived 10 years 161 patients with epithelial cancer and 15 patients with granulosa cell tumor who have survived 10 years group A have been compared with 157 patients with epithelial cancer and 14 patients with granulosa cell tumor who have not survived 10 years group B The study showed that among epithelial tumors the stage of tumor and the histological picture in the form of low potential malignancy or adenocarcinoma was of decisive importance for 10 years survival No correlation between information such as age marital status profession duration of symptoms and the nature of symptoms and 10 years survival could be found in patients with tumor in stages I and II Neither could the gynaecological examination the nature of the surgical treatment nor radiation therapy be correlated with 10 years survival in stages I and II 3 of the 152 patients with epithelial cancer in stages I and II who have survived 10 years have either died from their ovarian disease or have later on developed cancer localized to cervix or corpus uteri The author points out the risk of not removing both ovaries as well as the uterus and recommends that such patients are followed for many years after the treatment In 9 patients with granulosa cell tumor neither the medical history the stage of the tumor nor the treatment could be correlated with 10 years survival

INTRODUCTION

Randall (26) has found in the State of New York that the risk that a woman at some time or other in her life will develop cancer in cervix uteri corpus uteri or in the ovaries is 2 2% 1 5% and 1% respectively The same author states that the risk that the death of a woman will be caused by the mentioned disease is 0 4% 0 2% and 0 9% respectively These figures show that ovarian cancer though being the rarest of the three mentioned kinds of tumor causes the highest number of gynaecological cancer deaths

In spite of the great efforts to improve the prognosis in patients with ovarian cancer by more extensive surgical operations pre and postoperatively high voltage therapy and cytostatic treatment the prognosis at these tumors is still poor and in several of the patients with ovarian cancer a recurrence of the disease has taken place later than 5 years after the primary treatment Randall (26) The author has in this work tried to elucidate the characteristics of patients with cancer of the ovari who have survived more than 10 years especially with regard to the stage of tumor at the time of operation

MATERIAL AND METHODS

In Denmark all cases of cancer must be reported to the Danish Cancer Register This study comprises all women with histologically verified epithelial cancer or with granulosa cell tumor in the ovary who in the period 1943–57 were reported from the city of Copenhagen and Copenhagen and Frederiksberg county A total of 1 165 patients with epithelial ovarian tumors and 29 patients with granulosa cell tumors were registered in the area mentioned between 1943–57

This study comprises all patients who have survived 10 years 161 patients with epithelial tumor and 15 patients with granulosa cell tumor These two groups of patients are designated group A The control group called group B consists of 157 patients with epithelial tumors randomized among the 1 004 patients who have not survived 10 years and 14 patients with granulosa cell tumor who neither have survived 10 years

All the records of the patients have been reviewed by the author and the information below has been procured from these records

(*a*) Age marital status profession tumor diagnosed at the prophylactic examination or because of symptoms not related to the abdomen/tumor diagnosed because of symptoms from the abdominal disease previous operation for

Table I *Distribution of age in patients with primary epithelial carcinoma of the ovary and relationship between stage of the disease and distribution of age*

Age	Total				Stage I				Stage II			
	(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not alive at 10 years	
	No	%	No	%	No	%	No	%	No	%	No	%
Less than 10	0	0	0	0	0	0	0	0	0	0	0	0
10–19 years	1	0 6	2	1 3	1	0 7	1	2 9	0	0	1	2 7
20–29 years	5	3 1	2	1 3	5	3 7	1	2 9	0	0	0	0
30–39 years	24	14 9	7	4 5	19	14 1	3	8 8	4	18	2	5 4
40–49 years	49	30 4	42	26 8	41	30 4	7	0 6	8	36 4	5	13 5
50–59 years	52	32 3	48	30 6	43	31 9	10	29 4	7	31 8	16	43 2
60–69 years	25	15 5	44	28 0	21	15 6	10	29 4	2	9 1	11	29 7
70–79 years	4	2 5	11	7 0	4	3 0	2	5 9	1	4 5		5 4
80–89 years	1	0 6	1	0 6	1	0 7	0	0	0	0	0	0
	161	100	157	100	135	100	34	100	22	100	37	100
χ^2	$p<0\ 05$				$p>0\ 05$				$p>0\ 05$			

benign ovary disease (yes/no) duration of symptoms and nature of symptoms

(*b*) Objective findings at preoperative gynaecological examination clinical stage peroperative rupture of tumor (yes/no)

(*c*) The nature of the surgical operation radiation treatment (yes/no)

(*d*) Histological type tumor tissue detected in both ovaries (yes/no) tumor tissue detected in the endometrium (yes/no) and for epithelial tumors also the histological picture ("low potential malignancy /adenocarcinoma)

(*e*) Possible cause of death secondary tumor detected (yes/no)

Profession When grouping according to profession the division proposed by Svalastoga (29) was used

Clinical stage The division of stage was made according to the division into four stages proposed by the International Federation of Gynaecology and Obstetrics (FIGO) (9) As the study was made retrospectively it has been difficult to classify the tumor in several of the patients In cases of doubt between two possible stages the tumor was placed at the stage with the poorest prognosis The presence of tumor cells was not proved in the ascitic fluid of patients with tumor in stage I c because such an examination was only rarely carried out

Histology A histological examination of the tumor was made in all patients by 31 different pathologists but the slides were not reviewed The material is divided into epithelial tumors and granulosa cell tumors As only 57 of a total of 318 patients with epithelial tumors could be classified as serous mucinous endometrioid or mesonephric as proposed by FIGO (9) a correlation between these types and 10 years survival was not made Distinction was made between tumors that showed low potential malignancy and adenocarcinoma The first mentioned group consists of a transition stage between benign and malignant ovary tumors and have been included because these tumors must be treated as a neoplastic disease which might lead to the death of the patient Kottmeier (17)

Treatment Laparotomy was performed in all patients 200 patients with epithelial tumor and 17 patients with granulosa cell tumor received radiation treatment All these patients were irradiated on two dorsal and two ventral areas 203 received a dosage under 8 000 R and 9 received a dosage over 8 000 R 17 patients were additionally given radium therapy None of the patients received cytostatic treatment

Collection of information The patients included in the study were given a serial number at random prior to the collection of record information The purpose was to reduce the influence which knowledge of the survival of the patients might have had on the information recorded.

Statistical analysis To evaluate whether a characteristic appeared more frequently in one of the two study groups than in the other a χ^2 test was used The 5% limit has been applied as a level of significance In cases where significant difference was found between group A and B the epithelial tumors were divided according to stage. A re investigation was then made to see whether a difference could be found between group A and B Comparison between group A and B could not be made among patients with tumor in stage III–IV due to the small number of patients in group A (Table III)

RESULTS

Epithelial tumors

Characteristics that showed Statistical Difference between group A and B

Distribution on age Table I shows the distribution of age There is a significant difference between group A and B because there are more young and fewer old patients in the first group This differ

-IV

: rs	(B) Not alive at 10 years	
	No	%
	0	0
	0	0
	1	1 2
	2	2 3
	30	34 9
	22	25 6
	23	26 7
	7	8 1
	1	1 2
	86	100

nce cannot be found after division according to age

Symptoms Table II shows those symptoms re corded to be most frequent by Wetterdal (31) The able shows that only symptoms such as poor general condition constipation diarrhoea and vomiting showed a different incidence in the two groups as these symptoms were most frequent in group B This difference could not be found after division according to stage table II In stage II pollakisuria was found more frequently in group B than in group A

Gynaecological examination preoperative Mobility In 41 patients in group A and in 60 patients in group B the mobility of the tumor was evaluated preoperatively at a gynaecological examination In group A the tumor was found mobile in 26 patients 63 4%) and fixed in 15 (36 6%) In group B the corresponding figures were 19 (31 7%) and 41 3%) This difference is significant as the mobile s were most frequent in group A In stage I tumor was found mobile in 23 patients (67 6%) group A and in 8 (57 1%) in group B This differ is not significant In stage II the number of nts in which the mobility of the tumor was aluated was too small to make a statistical cal ion possible

Consistency The consistency of the tumor was evaluated in 83 patients in group A and in 90 patients in group B In group A the tumor was found cystic in 54 patients (65 1%) and solid in 29 (34 9%) In group B the corresponding figures were 40 (44 4%) and 50 (55 6%) The difference is significant as cystic tumors occurred more frequently in group A and solid tumors more frequently in group B In stage I the tumor was found cystic in 44 patients (65 7%) in group A and in 10 (56 6%) in group B This difference is not significant In stage II the number of patients where the consistency of the tumor was evaluated was too small to make a statistical calculation

The size of the tumor In all patients in group A and B the size of the tumor was evaluated preoperatively In 89 patients (55 2%) in group A a tumor that measured more than 10 cm in diameter was found and in 51 patients (31 7%) a tumor that measured less than 10 cm in diameter was found In 21 patients (13 1%) the tumor was not detected preoperatively In 100 patients (63 8%) in group B a tumor that measured more than 10 cm in diameter was found and in 37 patients (23 7%) a tumor that measured less than 10 cm in diameter was found In 20 patients (12 5%) the tumor was not detected preoperatively The difference between the two groups is not significant

The surface of the tumor In 44 patients in group A and in 83 patients in group B the surface of the tumor was evaluated preoperatively In group A the surface of the tumor was found to be uneven in 30 patients (68 2%) and even in 14 (31 8%) The figures in group B was 69 (83 1%) and 14 (16 9%) This difference is not significant

Clinical stage Table III shows group A and B divided according to stage The table shows that 157 patients (97%) in group A and only 71 (45%) in group B had a tumor in stage I and II The table also shows that difference in the distribution of stage I a I b and I c could not be detected between group A and B Similarly a difference in the distribution of stage II a and II b could not be detected

Surgical treatment Table IV shows that the surgical treatment was different in group A and B But this difference could neither be found in patients with tumor in stage I nor II (Table IV)

Peroperative rupture In 160 patients in group A and in 135 patients in group B it was stated whether the tumor had ruptured at the operation or not Rupture occurred in 38 patients in group A (23 8%) and in 65 (48 1%) in group B which is significantly more frequent in group B In patients with tumor in stage I rupture occurred in 58 (43 3%) in group A and in 20 (62 5%) in group B This difference is not significant In patients with tumor in

Table II *Distribution of symptoms in patients with primary epithelial carcinoma of the ovary and relation between stage of the disease and symptoms*

Symptoms	Total					Stage I				
	(A) Alive at 10 years		(B) Not alive at 10 years		χ^2 test ($p<0\ 05$)	(A) Alive at 10 years		(B) Not alive at 10 years		χ^2 test ($p<0\ 05$)
	No	%	No	%		No	%	No	%	
Abdominal pain	91	56 5	90	57 3	–	75	55 6	21	61 8	–
Heavy feeling in lower abdomen	31	19 3	29	18 5	–	25	18 5	6	17 6	–
Pollakisuria	36	22 4	45	28 7	–	31	23 0	11	32 4	–
Loss of weight	32	19 9	42	26 8	–	26	19 3	5	14 7	–
Increased girth of the abdomen	62	38 5	58	36 9	–	53	39 3	15	44 1	–
Abdominal tumor	19	11 8	13	8 3	–	15	11 1	3	8 8	–
Metrorrhagia	36	22 4	32	20 4	–	8	20 7	8	23 5	–
Poor general condition	40	24 8	65	41 4	+	36	26 7	9	6 5	–
Constipation	24	14 9	40	25 5	+	20	14 8	5	14 7	–
Diarrhoea	5	3 1	15	9 6	+	4	3 0	1	2 9	–
Vomiting	4	2 5	16	10 2	+	4	3 0	2	5 9	–
Total	161	100	157	100		135	100	34	100	

rupture occurred in 8 patients (36%) in group A and in 10 (27%) in group B This difference is not significant

Histology Table V shows that tumors of the type low potential malignancy was more frequent in group A than in group B and that this difference also could be detected in patients with tumor in stage I and II

Metastases to the other ovary In patients with tumor in stage I both ovaries were histologically examined in 59 patients in group A and in 16 patients in group B Tumor tissue was detected in both in 18 patients (30 5%) in group A and in 11 7%) in group B This difference is significant as lateral disease was most frequently detected in group B In patients with tumor in stage II tumor tissue was detected in both ovaries in 9 patients (64%) in group A and in 11 (67%) in group B This difference is not significant

Characteristics that did not show any Statistical Difference between Group A and B

Marital status 99 patients (61 4%) in group A were married and 62 (38 6%) unmarried or previously married The corresponding figures in group B was 100 (63 8%) and 57 (36 2%) This difference is not significant

Profession 1 patient (0 8%) in group A belonged to the upper class 63 (39 2%) to the middle class and 97 (60 0%) to the lower class 64 patients (40 8%) in group B belonged to the middle class 93 (59 2%) to the lower class This difference is significant

Reason for admission In 16 patients (9 9%) group A the ovary disease was diagnosed at a p phylactic examination or by an examination another complaint not related to the abdom while 145 (90 1%) were examined because of sym toms from their disease The corresponding figu in group B was 14 (8 9%) and 143 (91 1%) T difference is not significant

Duration of symptoms 47 patients (30 7%) group A had had symptoms for less than 3 mont 43 (28 1%) for 3–5 months and 63 (41 7%) for m than 5 months The corresponding figures in gro B was 60 (39 2%) 32 (20 9%) and 61 (39 9%) 12 patients the duration of symptoms could not estimated The difference between group A and B not significant

Previous operation for benign ovary disease patients were previously operated for benign ova disease 9 belonged to group A and 11 to group B

Radiation therapy 94 patients (58 4%) in gro A and 106 patients (67 5%) in group B had receiv radiation therapy This difference is not significan

Metastases proved in the endometrium In 9 of patients examined in group A and in 5 of 45 e amined in group B tumor tissue was detected in t endometrium This difference is not significant

II

Alive 10 years	(B) Not alive at 10 years		χ^2 test	Stage III–IV (A) Alive at 10 years	(B) Not alive at 10 years	
%	No	%	($p<0.05$)	No	No	%
63 6	18	48 6	–	2	51	59 3
22 7	11	29 7	–	1	12	14 0
18 7	16	43 2	+	1	18	20 9
18 7	9	24 3	–	2	8	32 6
36 4	17	45 9	–	1	26	30 2
13 6	6	16 2	–	1	4	4 7
27 3	9	24 3	–	2	15	17 4
18 2	14	37 8	–	0	45	52 3
13 6	10	27 0	–	1	25	29 1
4 5	3	8 1	–	0	11	12 8
0	4	10 8		0	10	11 6
100	37	100		4	86	100

l tumor tissue was proved in 5 out of 44 patients examined with tumor in stage I

Calculation of 10 years survival The study showed that the clinical stage and the histological picture of the tumor in the form of low potential malignancy or adenocarcinoma was of decisive importance to the 10 years survival As group B is randomized among all patients who have not survived 10 years and therefore must be presumed to constitute a representative section of the patients who have not survived 10 years it is possible to estimate 10 years survival in consideration of clinical stage and histological picture by means of the below formula

Table III Distribution of stage of the disease in patients with primary epithelial carcinoma of the ovary

	(A) Alive at 10 years		(B) Not alive at 10 years	
	No	%	No	%
Stage I	135	83 8	34	21 7
Stage II	22	13 6	37	23 6
Stage III	4	2 6	85	54 1
Stage IV			1	0 6
Total	161	100	157	100
χ^2	$p<0.05$			
Stage I a	92	68 9	18	5 9
Stage I b	32	23 0	10	29 5
Stage I c*	11	8 1	6	17 6
Total	135	100	34	100
χ^2	$p>0.05$			
Stage II a	4	22 7	9	4 3
Stage II b	18	77 3	28	75 7
Total	22	100	37	100
χ^2	$p>0.05$			

* Ascitic fluid not examined for tumor cells

X [illegible]

X = number of patients with survival a clinical stage y and histological picture z

n = total number of patients with survival a

y = the presence of patients with tumor in stage y in patients with survival a

z_a = the presence of histological picture z in patients with tumor in stage y and survival a

The results of these calculations will appear from Table VI

Cancer in other primary sites 33 patients (20%) in group A and 10 (6%) in group B have after treatment for ovarian cancer been treated for cancer in another site Cancer of the corpus uteri had been

Table IV *Distribution of surgical treatment in patients with primary epithelial carcinoma of the ovary a relationship between treatment and stage of the disease*

	Total				Stage I				Stage II			
	(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not al at 10 years	
	No	%	No	%	No	%	No	%	No	%	No	%
Explorative laparotomy and diagnostic biopsy	1	0 6	47	29 9	1	0 7	0	0	0	0	5	13 5
One ovary removed	59	36 6	30	19 1	56	41 4	9	26 6	3	13 7	9	ʼ4 3
Both ovaries removed	43	26 7	38	24 2	35	26 0	15	44 1	8	36 4	6	16 3
One ovary and uterus removed	9	5 6	6	3 8	8	5 9	2	5 8	1	4 5	3	8 1
Both ovaries and uterus removed	49	30 5	36	23 0	35	26 0	8	23 5	10	45 4	14	37.8
	161	100	157	100	135	100	34	100	ʼ2	100	37	100
x^2	$p<0\ 05$				$p>0\ 05$				$p>0\ 05$			

detected in 10 patients in group A cancer of the cervix uteri in 6 patients and cancer outside the genitalia in 17 patients In group B 2 patients had developed cancer of the uterine body and 8 patients cancer outside the genitalia after the treatment for cancer ovarii It was not possible to distinguish between metastases and a second primary cancer

Cause of death 55 patients who have survived 10 years at the conclusion of this study are dead 43 of these patients were originally treated for a tumor in stage I In 12 (28%) the cause of death was ovarian cancer 12 of the 55 patients who died were ginally treated for a tumor in stage II In 4 pa ts the cause of death was cancer of the ovary 4 tients with tumor in stage III and IV are still alive In group B all patients are dead The cause of death was cancer of the ovary in 20 (59%) patients with tumor in stage I in 27 (73%) with tumor in stage II and in 74 (86%) with tumor in stage III–IV 36 patients died from other disease

Granulosa cell tumors

None of the recorded characteristics showed a significant difference between 15 patients with granulosa cell tumor who had survived 10 years group A and 14 patients who had not survived 10 years group B

Age The average age in group A was 47 5 years and in group B 51 6 years

Marital status 9 patients (60%) in group A were

Table V *Distribution of histological picture in patients with primary epithelial carcinoma of the ovary and its relation to the stage of the disease*

	Total				Stage I				Stage II			
	(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not alive at 10 years		(A) Alive at 10 years		(B) Not alive at 10 years	
	No	%	No	%	No	%	No	%	No	%	No	%
Low potential malignancy	57	38 5	4	2 7	49	39 2	2	6 5	7	35 0	1	2 9
Adenocarcinoma	91	61 5	145	97 3	76	60 8	29	93 5	13	65 0	33	97 1
	148	100	149	100	125	100	31	100	˛0	100	34	100
x^2	$p<0\ 05$				$p<0\ 05$				$p<0\ 05$			

II+IV		
e ars	(B) Not alive at 10 years	
	No	%
	4?	48 7
	1?	14 0
	17	19 8
	1	1 ?
	14	16 3
	86	100

ried and 6 (40%) unmarried or previously mar | The corresponding figures in group B was 8 %) and in 6 (36%) This difference is not signifi t

rofession 7 patients (47%) in group A belonged he middle class and 8 (53%) to the lower class corresponding figures in group B were 7 (50%) 17 (50%)

Reason for admission In 3 patients (20%) in up A the ovary disease was detected at a prophy ic examination or at an examination for another nplaint not related to the abdomen and 12 (80%) e examined because of symptoms due to their lominal disease In group B the corresponding ires were 3 (21%) and 11 (79%)

Duration of symptoms 4 patients (27%) in group A had had symptoms for less than 3 months 5 (33%) from 3–5 months and 6 (40%) for more than 5 months In group B the corresponding figures were 6 (43%) 4 (29%) and 4 (28%) Table VII shows that the most frequent symptom was me trorrhagia None of the symptoms occurred with significantly different frequency in the two groups

II+IV		
ve ars	(B) Not alive at 10 years	
	No	%
	1	1 2
	83	98 8
	84	100

Gynaecological examination 8 patients (52%) in group A were found at the preoperative gynaeco logical examination to have a tumor with a diameter of more than 10 cm 5 patients (35%) were found to have a tumor of less than 10 cm in diameter while the tumor was not detected in 2 (13%) The cor responding figures in group B were 9 (64%) 4 (29%) and 1 (7%) This difference is not signifi cant The consistency mobility and surface of the tumor was examined in so few patients that a com parison between group A and B was not possible

Clinical stage Table VIII shows that in group A there is a predominance of patients with tumor in stage I but the difference between group A and B is not significant

Operative treatment 5 patients (33%) in group A had had a unilateral oophorectomy and 5 (33%) bilateral oophorectomy 1 (7%) unilateral oophor ectomy and hysterectomy and 4 (27%) bilateral oophorectomy and hysterectomy In group B 1 pa tient (7%) had had an explorative laparotomy 4 (28%) unilateral oophorectomy 5 (37%) bilateral oophorectomy and 4 (28%) bilateral oophorectomy and hysterectomy There is not a significant differ ence between group A and B

Radiation therapy 5 patients (33%) in group A and 7 (50%) in group B received radiation therapy This difference is not significant

Metastases to the opposite ovary In group A tumor tissue was detected in both ovaries in 3 out of 6 patients examined and in group B in 1 out of 5 patients examined

Cancer in other primary sites Cancer was de tected in 2 patients after the treatment for ovarian cancer In 1 patient in group A cancer of the uterine body was diagnosed and in 1 patient in group B cancer of the cervix was diagnosed It was not possible to distinguish between metastases and a second primary cancer

Cause of death 3 patients in group A are dead at the conclusion of this study In 1 patient the cause of death was cancer of the ovary In 10 patients (71 4) in group B where all patients are dead the cause of death was cancer of the ovary

Table VI *Relationship between 10 years survival stage of the disease and histological picture in patien with primary epithelial carcinoma of the ovary*

Stage	No	%	Survival	No	%	Low potential malignancy No	Low potential malignancy %	Carcinoma No	Carcinoma %
I	353	30	Alive at 10 years	135	38	53	79	82	29
			Not alive at 10 years	218	62	14	21	04	71
			Total	353	100	67	100	286	100
II	259	22	Alive at 10 years	22	8	8	53	14	6
			Not alive at 10 years	237	92	7	47	230	94
			Total	259	100	15	100	244	100
III+IV	553	48	Alive at 10 years	4	0 7	1	13	3	0 1
			Not alive at 10 years	549	99	7	87	542	99 9
			Total	553	100	8	100	545	100
Total	1 165	100							

DISCUSSION

Epithelial tumors

The purpose of this study was to investigate what differences could be proved between all patients with ovarian cancer who have survived 10 years group A and those who have not survived 10 years group B in a geographically limited area The most significant difference between the two groups was that 84% of the patients in group A had a tumor in stage I and 16% a tumor in stage II–IV while in group B 22% had a tumor in stage I and 78% a tumor in stage II–IV A major part of the other differences between group A and B could be ex ned as being due to this dissimilar composition the two groups Thus a difference in distribution of age the more frequent appearance of symptoms such as poor general condition vomiting constipation and diarrhoea the more frequent appearance of solid and fixed tumors and the higher frequency c operative ruptures in group B than in group could like the actual difference in surgical trea ment be explained as being due to the dissimila representation of patients with tumors in differer stages in group A and B The correlation foun between clinical stage and 5 years survival has pre viously been shown by Mackey & Sellers (18) Munnel (22) Nieminan & Purola (24) and Pomme rence & Molts (25) The latter also found a marke decrease in 10 years survival from stage I–IV In th present study no difference in 10 years surviva could be found in the distribution of stage Ia Ib and Ic and stage IIa and IIb among patients with tumor in stage I and II respectively In agree ment with this Aure et al (2) and Kottmeier (13) could not show a clear decrease in prognosis from stage Ia to Ic The first mentioned found the same

Table VII *Distribution of symptoms in patients with granulosa cell tumors*

Symptoms	Alive at 10 y (15 pats) No	Alive at 10 y (15 pats) %	Not alive at 10 y (14 pats) No	Not alive at 10 y (14 pats) %
Abdominal pain	6	40 0	6	42 9
Pollakisuria	3	20 0	3	21 4
Loss of weight	1	6 7	1	7 1
Increased girth of the abdomen	1	6 7	1	7 1
Tumor in the abdomen	1	6 7	0	0
Metrorrhagia	9	60 0	10	71 4
Poor general condition	3	20 0	5	35 7
Constipation	0	0	2	14 3

Table VIII *Distribution of the stage of disease in patients with granulosa cell tumors*

	Group A Alive at 10 years		Group B Not alive at 10 years	
Stage	No	%	No	%
I	17	80 0	8	57 2
II	3	20 0	3	21 4
III	0	0	3	21 4
IV	0	0	0	0
Total	15	100	14	100

survival in stage I b and I c while the latter found a better prognosis in stage I c than in I b The fact that the ascitic fluid was not examined for tumor cells in the present study renders a direct comparison impossible Kottmeier (13) found a better prognosis in stage II a than in II b which could not be shown in the present study The histological picture of low potential malignancy or adenocarcinoma has in the present study been of importance for the 10 years survival both in stage I as well as in stage II (Table I) The better prognosis in the first mentioned group is previously shown by Aure et al (2) and Kottmeier (12) Table VI shows the estimated distribution of patients in stage I II and III–IV in the total population examined and shows that knowledge of the histological picture as well as clinical stage gives a more varied picture of the chance of surviving 10 years than a prognosis merely calculated on the basis of stage

A poor prognosis of cancer of the ovary in elderly women was previously found by Mackey & Sellers (18) and Pomerence & Moltz (25) The difference in distribution on age between group A and B is in this work due to the fact that elderly women more frequently had a tumor in stage III–IV than younger women Women over 60 years of age made up 39% of the patients with a tumor in stage III–IV and only 4% in stage I–II The poorer prognosis in married women than in unmarried women found by Stone et al (28) could not be shown neither was a correlation between profession and prognosis found In Stone et al (28) the duration of symptoms could not be related to the prognosis nor was this possible in the present study Neither was it possible to show a better prognosis in patients in whom the tumor was diagnosed at a prophylactic examination Only symptoms indicating a widespread tumor table II were more frequent in group B than in group A but a difference in symptoms could not be found after the distribution according to clinical stage As found by Mackey & Sellers (18) Munnel (21) and Turner et al (30) the most frequent symptoms were pain in the abdomen and abdominal swelling (Table II) The preoperative gynaecological examination forms part of the evaluation of all patients with cancer of the ovary In the present study the size of tumor and the nature of the surface could not be related to 10 years survival but cystic and mobile tumors were found more frequent in group A than in group B This difference could however not be found when distributing the patients according to clinical stage

Aure et al (1) Grogan (6) Mackey & Sellers (18) and Munnell et al (20) found that operative rupture with subsequent risk of intraperitoneal spread did not alter the prognosis In the present study a correlation between operative rupture and 10 years survival could neither be found in stage I nor II

Long et al (16) Kent & Mackey (10) Munnell (22) and Pomerence & Moltz (25) found a better prognosis in patients where both ovaries and uterus were removed at the primary operation In stage I a the effect of this extensive surgical operation is however doubtful (Barnes (3) Munnell (23) and Kottmeier (14)) This is particularly the case in patients where the tumor shows a histological picture of low potential malignancy (Kottmeier (14)) In the present study only 25% of the patients with a tumor in stage I and 41% of the patients with a tumor in stage II had both ovaries and uterus removed and the surgical treatment did not have any decisive influence on 10 years survival A difference in the surgical treatment between group A and B could neither be detected in stage I nor II table IV Cancer of the ovary frequently shows metastases to the opposite ovary even though the process is macroscopically unilateral (Munnell (23)) and metastases can be found in the endometrium (Kottmeier (14) and Lynch & Dockerty (17) In the present study bilateral involvement of the ovary was shown in 29 of 75 patients examined with tumor in stage I and metastases to the endometrium were shown in 5 out of 44 patients examined in this stage The fact that 18 patients after the treatment for ovarian cancer have developed cancer in the uterus or have had metastases in the uterus indicates the risk of not removing the uterus at the primary operation

Opinions differ as to the effect of postoperative radiation therapy Latour & Davis (15) Aure et al (1) and Kottmeier (12) have found a better 5 years survival after radiation therapy to patients with tumor in stage I than if radiation therapy was not given whereas Munnell & Taylor (19) do not share this view on the contrary all the mentioned authors recommend radiation therapy to patients with tumor in stage II–IV In the present study in which 63 % of the patients had received radiation therapy most often a dosage under 8000 R a correlation with 10 years survival could not be shown A more close evaluation of the benefit of radiation therapy must take place in the light of a distribution into serous mucinous endometrioid and mesonephric tumors as their sensitivity to radiation seems to vary The effect of the modern high voltage treatment may also be more effective than the relatively small dosages used in this study

33 of the 161 patients who have survived 10 years in this study have later developed a new cancer or recurrence most often in the uterus and in 16 of 55 patients who died more than 10 years after treatment for cancer in the ovary the cause of death was the primary disease The author must therefore recommend that patients treated for ovarian cancer should be seen for many years after the primary treatment due to the risk of further cancer or late recurrence

Granulosa cell tumors

The most pronounced features of the study was that of the characteristics examined showed ificant differences in group A and B Busby et al (4) found a better prognosis in stage I but in the present study in which 80 % in group A and 57 % in group B had tumor in stage I this difference was not signficant The better prognosis found by von Herold (8) Kjellgren (11) Munnell (22) and Sjøstedt & Wahlin (27) in patients with granulosa cell tumors than in patients with epithelial tumors was also found in the present study in which 51 % in the first mentioned group and only 13 8 % in the last mentioned group have survived 10 years In the present study the average age was around 50 years this was also found by Busby et al (4) Sjøstedt & Wahlin (27) found that symptoms such as pain and loss of weight were prognostically bad but neither these nor the most frequent symptom metrorragia could in the present study be related to 10 years survival It is remarkable that this hormone producing tumor had reached a size of 10 cm i diameter or more in 59 % of the patients This co responds to the findings in patients with epitheli tumors Both Munnell (23) and Sjøstedt & Wahli (27) state that the risk of recurrence is small i patients with the disease localized to only one ova ry and they find that unilateral oophorectomy i indicated in young women who have a desire fo children In this study in accordance with this better prognosis could not be found after bilater oophorectomy and hysterectomy Diddle (5) foun that granulosa cell tumors are sensitive to radiation but Haines & Jackson (7) and Sjøstedt & Wahli (27) could not show a better prognosis after radia tion therapy The last mentioned finding is con firmed in the present study

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CORRELATION OF MATERNAL PHYSICAL FITNESS DURING PREGNANCY WITH MATERNAL AND FETAL pH AND LACTIC ACID AT DELIVERY

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Abstract The physical fitness of 1–0 healthy primigravidae was determined two weeks before term using first the standardized three stage submaximal work test and on the following day the voluntarily maximal pulse-conducted work test on a bicycle ergometer After the first test the level of lactic acid in the capillary circulation of 115 mothers was examined Immediately after delivery the pH and the level of lactic acid in the maternal artery umbilical vein and umbilical artery were determined The level of lactic acid after the work test was negatively correlated with the physical performance of the mother The level of lactic acid in the mother after the work test and the levels of lactic acid in the umbilical vessels were positively correlated The mean pH value in physically fit women after delivery was almost significantly higher than in the women of below average performance The pH level in the umbilical artery was also almost significantly higher in the mothers with above average performance The physically fit women appear to work more during delivery than the less fit mothers as the level of lactic acid after the delivery was as high as or higher than in mothers with a physical performance below average The physical fitness of six mothers who delivered an asphyxiated baby was almost significantly lower than the performance of the mothers Five mothers with an exceptionally high pH after delivery had a significantly higher performance than the other mothers

During the last twenty years there has been a considerable increase in the understanding of biochemical environment in the mother and fetus during labor The changes in pH and blood gas levels at the time of delivery have been presented descriptively in several publications (1 9 10 11) However analysis of the reasons for the changes still continues One point of view is to approach labor in terms of physical performance of the mother

In work physiology it is well known that physically fit subjects can perform a standardized work load with a less notable increase in acidic products and with less of decrease in pH than physically unfit subjects (4 16) Also labor is a form of work for the mother However there are no earlier investigations on the correlation of the physical fitness of the mother and the levels of pH or lactic acid in the mother and fetus or newborn Therefore the topics of investigation in this study were

1) formation of lactic acid in the mother in a standardized work test in late pregnancy

2) levels of pH in the mother and newborn after delivery in correlation with the physical performance of the mother

3) levels of lactic acid in the mother and in the newborn after delivery in correlation with the physical performance of the mother

SUBJECTS AND METHODS

1–0 healthy primigravidae aged 0 to 6 years were accepted to take part in the study and gave their consent when informed The physical fitness of the mothers was determined two weeks before term using two types of work tests on the bicycle ergometer The first test was a submaximal three stage test with loads of 150 300 and 450 kpm/min each lasting four minutes in succession (15) The second test the next morning was a pulse-conducted triangular ECG test developed by Arstila (2) The circumstances in the test laboratory and the principles of the tests are described in two earlier papers (6 7)

Immediately after the first test a blood sample of 00 µl was collected from the tip of the warmed middle finger after a deep stab without squeezing ($n = 115$)

The deliveries of these mothers were followed and immediately after delivery before the first breath of the newborn the umbilical cord was closed with two clamps and blood samples were taken separately from the umbilical vein (UV) and the umbilical artery (UA) S

Table I *The results of the work tests ±S D (n=120)*

√TW 19%	95 9±11 8
WL/HR 19%	106 8±19 2
Mean physical fitness %	101 2±14 2
Åstrand s index ml/kg min	40 7± 8 5

ously a blood sample from the maternal radial artery (MA) was also drawn The samples were taken anaerobically in sterile heparinized polyethylene syringes of 5 ml after which the syringes were sealed and placed in ice water

The pH readings were made on an IL (113 ST) pH blood gas analyzer after calibrating the electrode with Radiometer Copenhagen buffer solutions (7 381 and 6 840 at 38 C) The standard deviation of a single measurement was ±0 007 pH units when analysis were performed in duplicate

The blood samples of 200 μl for the determination of the lactic acid were stabilized with 400 μl of ice-cold perchloric acid shaken and stored at +4 C until analyzed The samples remain unchanged for at least 5 days For the quantitative determinations the commercially available enzymatic test (Biochemia Boehringer) was used with minor modifications in the technique suggested by the manufacturer The reliability of the single determination was ±0 04 mmol/l

The statistical analysis of the results was performed at the Department of Applied Mathematics of the University of Turku on a Univac 1108 computer

RESULTS

The results of the work tests are presented in Table I The mean concentration of the lactic acid after first work test was 3 20±1 08 (S D) mmol/l a range of 1 40 to 7 35 mmol/l The correla between the results of the work tests and the lactic acid concentration are shown in Table II All correlations are inversely very significant The mean pH values after delivery are presented in Table III In Table IV the pH values are correlated with the results of the pulse conducted triangular ECG test when the mothers have been divided into four subgroups according to the results in the work test When the physical fitness is presented as WL/HR 19% or as mean physical fitness % the pH value in the MA is almost significantly higher in the groups with a physical fitness of more than 110% than in the groups with a physical fitness of 91–100% (p values <0 05) When the physical fitness is presented as a percentage of mean physical fitness the pH value in the UA is almost significantly higher (p <0 05) in the groups with physical fitness of more than 100% (pH 7 33±0 07 n=55) than in the group of 100% or below (pH 7 30±−0 07 n=65)

In six cases the pH value in UV and in UA was lower than two standard deviations from the mean value The physical performance of those mothers is compared with that of other mothers in Table V and it is shown that the fitness is almost significantly lower Five mothers had an abnormally high pH diverging more than two standard deviations from the mean pH value The physical fitness of those mothers is compared in Table with that of other mothers and the fitness i significantly higher

The concentrations of lactic acid after delivery are presented in Table III There are no significant differences between the levels Instead all concentrations found after the delivery are very significantly higher than the concentrations after the first work test (p<0 001) The correlations between the lactic acid concentrations are presented in Table VIII It can be seen that the correlation between the concentrations in maternal capillary blood after the work test and in maternal arterial blood after the delivery is not significant but there is an almost significant positive correlation between the concentrations in the mother after the work test and in UV and UA after the delivery (p<0 05) The correlations between the lactic acid levels in the maternal and umbilical vessels after delivery are very significant (p<0 001) The concentration of lactic acid in MA after delivery was in 54 8% of all deliveries higher than in UV and in 51 7% of deliveries higher than in UA In Table VIII the parturients have been divided in two groups according to the results in pulse conducted ECG test When the mean values are compared it is found that the correlation of lactic acid in MA

Table II *The correlations between the results of the work tests and the concentration of lactic acid after the work test (n=115)*

	Correlation coefficient	p
√TW 19%	−0 425	<0 001
WL/HR 19%	−0 452	<0 001
Mean physical fitness %	−0 489	<0 001
Åstrand s index	−0 327	<0 001

Table III *The levels of pH (±S D) and lactic acid (±S D) in the maternal artery (MA) umbilical vein (UV) and umbilical artery (UA) after delivery*

	pH ($n=120$)			Lactic acid mmol/l ($n=120$)		
	Mean	S D	Range	Mean	S D	Range
MA	7 45	0 05	7 33–7 60	4 38	1 57	1 90–9 70
UV	7 37	0 07	7 10–7 49	4 02	1 63	1 95–9 40
UA	7 31	0 07	7 06–7 44	4 07	1 71	1 85–9 25

Table IV *The pH values in the maternal artery (MA) umbilical vein (UV) and umbilical artery (UA) after delivery correlated with the physical fitness of the mother ($n=120$)*

	≤90%	91–100%	101–110%	>110%
$\sqrt{TW}$ 19%	$n=40$	$n=41$	$n=23$	$n=16$
MA	7 44±0 04	7 44±0 05	7 46±0 06	7 45±0 06
UV	7 36±0 07	7 37±0 08	7 37±0 08	7 37±0 06
UA	7 30±0 07	7 32±0 08	7 32±0 08	7 32±0 06
WL/HR 19%	$n=19$	$n=35$	$n=22$	$n=44$
MA	7 44±0 04	7 44±0 04	7 44±0 05	7 46±0 06
UV	7 36±0 07	7 35±0 08	7 38±0 07	7 38±0 07
UA	7 31±0 07	7 30±0 08	7 31±0 07	7 33±0 07
Mean physical fitness %	$n=24$	$n=41$	$n=28$	$n=27$
MA	7 44±0 04	7 44±0 04	7 45±0 05	7 47±0 06
UV	7 36±0 07	7 36±0 08	7 37±0 08	7 38±0 06
UA	7 31±0 07	7 30±0 07	7 32±0 08	7 33±0 06

after the delivery is very significantly higher in the mothers whose $\sqrt{TW}$ 19% values were above average In the same group the concentration of lactic acid in UV was almost significantly higher (<0 05) than in the group with $\sqrt{TW}$ 19% below average Other differences are not statistically significant

Table V *Comparison between the physical fitness (±S D) of mothers with an abnormally low umbilical cord pH and the fitness of mothers with a normal umbilical cord pH post partum (Cochran s test)*

	Mothers with an abnormally low umbilical cord pH ($n=6$)	Mothers with a normal umbilical cord pH ($n=114$)	P
$\sqrt{TW}$ 19%	93 0±11 9	96 0±11 8	<0 05
WL/HR 19%	94 5± 8 8	107 1±19 6	<0 01
Mean physical fitness %	93 7± 8 9	101 6±14 4	<0 05

DISCUSSION

A decrease of pH in the mother and fetus during the end of the first stage and in the course of the second stage of labor is well documented (1 9 10 11) In the mother this has been attributed mainly to the accumulation of lactic acid as a result of uterine activity and the voluntary muscular efforts of the mother during labor (3 14) In the fetus the decrease of pH is generally of both a metabolic and respiratory type A notable lowering of pH in the fetus means a threat to fetal well being

The mean pH values found in this study are comparable with other studies (9 10 11) When the pH values are correlated with physical fitness a certain relationship is noticed The asphyxiated babies were delivered by mothers whose physical performance was lower than average The mothers with an exceptionally high pH after delivery in other words mothers with probable respiratory alkalosis tended to have better physical performance than average Also the normal pH values are in some distinct positively correlated with the physical fitness of the mothers

Table VI *Comparison between physical fitness (±S D) of mothers with abnormally high arterial pH and that of mothers with normal pH post partum (Cochran s test)*

	Mothers with abnormally high arterial pH (n=5)	Mothers with normal arterial pH n=115)	p
√TW 19%	106 4± 8 4	95 5±11 5	<0 01
WL/HR 19	122 6±14 0	105 8±19 3	<0 05
Mean physical fitness %	114 4± 8 8	100 6±14 2	<0 01

The question remains why the pH values of physically fit mothers and those of their babies are higher There are two possible explanations for the maternal values First the oxygenative system of the physically fit women could be more capable of eliminating CO_2 compared with the elimination rate in unfit mothers Second the physically fit mothers could be more capable of producting energy by means of the oxygenative system requiring less anaerobically produced energy The increase of acid metabolites which is found to occur during the second stage of the labor (3 9 14) would then be less

The pH changes in the fetus in normal labors are for the greatest part generated by maternal influences (3 9 14) but at the end of the second stage probably due to disturbances in utero-placental circulation an inadequate oxygen supply to the may occur (9) and the amount of H ions in the increases Thus the reasons for the higher of the newborn of fit mothers could be either the lower concentration of acid metabolites in the mother to transfer to the fetus or a better circulation in the uterus and placenta to produce the better

Table VII *The correlations between the concentrations of lactic acid in maternal arterialized capillary sample after the work test (MC work) in maternal radial artery after the delivery (MA) in umbilical vein (UV) and in umbilical artery (UA) (n=115)*

	MA	UV	UA
MC work	0 123	0 203	0 215
MA	–	0 638*	0 561*
UV	–	–	0 954*

p<0 05 * p<0 001

Table VIII *The comparison of lactic acid concentrations (±S D) in the groups of physi performance below and over normal (=100 n=120*

	≤100%	>100%	p
√TW 19%	n=76	n=39	
MA	4 04±1 34	5 05±1 79	<0 00
UV	3 79±1 51	4 49±1 77	<0 05
UA	3 85±1 63	4 51±1 80	n s
WL/HR 19%	n=50	n=65	n.s
MA	4 45±1 58	4 33±1 58	n.s
UV	4 17±1 75	3 91±1 54	n s
UA	4 23±1 80	3 95±1 6?	n.s
Mean physical fitness %	n=61	n=54	n s
	4 23±1 51	4 55±1 65	n s
	3 94±1 69	4 12±1 58	n s
	3 96±1 70	4 19±1 66	n s

n s =not significant

elimination of CO_2 from the fetal blood Support t the latter idea is given by the finding that placenta of fit women are significantly heavier than those o less fit women (Erkkola unpublished observation)

The lactic acid level in the three stage work tes of this study is negatively correlated with the phy cal fitness which was to be expected in light of other studies (4 16) When the lactic acid levels after the work test and after delivery are compared it can be seen that in any case labor has been harder work than 3 600 kpm in 12 minutes The lactic acid levels after delivery found in this study are well comparable with the results of other studies (9) especially since all parturients were primigravidae (3) The mean concentration of lactic acid in the mother 4 38 mmol/l after labor is not very high In some individual cases however concentrations of 7 to 9 mmol/l were found indicating that during the last minutes of labor the mother had an intensive anaerobic working period

If we compare the concentrations of lactic acid in the mother and in the umbilical vessels it becomes clear that in most cases the main source of the fetal lactic acid is the mother The lactic acid passes the placenta freely in monkeys (8) and it is presumed that a free crossing occurs in man as well (3 9) However it is also clear that in some cases due to hypoxia during the last minutes of labor the fetus produces its energy through anaerobic metabolism resulting in high levels of lactic acid in spite of low levels in the mother

When the lactic acid levels after the work test and after labor are correlated some interesting findings are made There is no significant correlation between the maternal concentrations Logically it could be presumed that the production of energy is of the same relative magnitude in the work during labor as in the work test When the correlation between the maternal lactic acid concentration after the work test and the concentrations in the umbilical vessels are calculated it is found that they are almost significant This finding is difficult to explain since the correlation between the maternal concentrations after test and labor was not significant in this material However it is known that during exercise the greater part of cardiac output circulates the working muscles Thus when pregnant women are exercising the circulation in the uterus diminishes and after the exercise the circulation overflow in the uterus occurs to compensate a possible insufficiency in the fetal oxygenation (5 12) The higher concentration of lactic acid in the mother after exercise may indicate a lower oxygenative capacity This may cause disturbances in the utero-placental flow during labor resulting in an elevated anaerobic metabolism in the fetus the products of which can not be eliminated by the mother after the delivery

When the levels of lactic acid in MA UV and UA are correlated with physical fitness an interesting finding is made The mean concentration of lactic acid in the mothers with $\sqrt{TW}$ 19% over 100% is significantly higher than that in mothers with a $\sqrt{TW}$ 19% below 100% Since the lactic acid level in the standardized work was lower in physically fit women than in unfit mothers the only explanation is that the mothers with higher $\sqrt{TW}$ 19% have been working more during delivery On the other hand there are no statistically significant differences between the levels of lactic acid when the physical fitness is presented as a percentage of WL/HR 19 or as a percentage of mean physical fitness These results show that the physically fit mothers do not produce less lactic acid than the less fit mothers during labor Therefore it could be presumed that they are working more during the second stage and especially during the period of expulsion of the baby This finding of similar or higher levels of lactic acid with fit mothers differs from the results of Stembera et al (13) who found that the lactate production was less in women who had a gymnastic program during the pregnancy when compared with sedentary mothers They did not however take the level after delivery but measured the rise of concentration every three hours during labor Also the difference began to be noticed after labor of 10 or more hours duration whereas in this study the mean duration of labor was about 7–8 hours (Erkkola unpublished observations)

Since the pH levels of fit women were higher than the pH levels of less fit women it logically follows that the respiration and oxygenative capacity of fit mothers compensate the higher or equal levels of lactic acid Five women with exceptionally high pH values and simultaneously with high physical capacity give support to this theory

The following conclusions from the results of this study can be made

1) The more the mother produces lactic acid during the standardized work test the higher are the concentrations of lactic acid in the umbilical vessels after the delivery

2) The pH in fit mothers is higher than the pH in less physically fit mothers after the delivery This is reflected to some extent in the fetal pH

3) The fit mothers perform as much anaerobic work during labor as the less fit mothers

4) The high levels of lactic acid and thus the metabolic acidosis were compensated by the high oxygenative capacity of the physically fit women

5) The mothers with low physical performance are more liable to have asphyxiated babies than the physically fit mothers

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CHANGES IN CARDIAC FUNCTION DURING AND AFTER PREGNANCY EXPRESSED BY SYSTOLIC TIME INTERVALS

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Abstract Hemodynamic changes during the first and third trimester in pregnancy and in the first week of puerperium were evaluated by non invasive measurements of Systolic Time Intervals (STI) in supine and left lateral position The Pre-ejection Period (PEP) was found to shorten significantly in pregnancy and the puerperium due to the increased blood volume The electro-mechanical systole (QS_2) and left ventricular ejection time (LVET) were shortened too while PEP/LVET ratio was increased in the third trimester due to the mechanical compression of the gravid uterus on the inferior vena cava. A lengthening of QS_2 and LVET and a decreased PEP and P/L ratio were demonstrated in the third trimester in lateral position when the pressure of the enlarged uterus was eliminated Heart rate (HR) increased in late pregnancy as well as after delivery while arterial blood pressure (BP) only underwent minor changes Employment of the STI seems to provide more useful information about the changes in cardiac function during gestation than HR and BP does The measurements of STI can be repeated without any risk or inconvenience to the patients

INTRODUCTION

Physiological changes develop in many organ systems during the course of gestation and parturition (7) The changes in the maternal cardiovascular system are related to hemodynamic volumetric hormonal and nutritional factors (22)

Cardiac output measured by either direct Fick principle (6) or by dye dilution technique (21) has shown an increase from the first trimester with a maximum between the 24th and 32nd week of gestation In late pregnancy cardiac output remains high unless the pregnant woman assumes a supine position (14) when the enlarged uterus compresses the inferior vena cava (9) and abdominal aorta (2) which can produce the supine hypotensive syndrome (13 18)

Evaluation of myocardial function by Systolic Time Intervals (STI) is based on the classic studies by Wiggers (27) and Katz and Feil (12) It is now commonly agreed that STI are useful as non invasive indices of cardiac function (4 5 25 26) The pre-ejection period (PEP) is closely related to the isovolumic concentration time (15) and left ventricular ejection time (LVET) vary directly with stroke volume (23) The ratio between PEP and LVET (PEP/LVET ratio) has been shown to be a semiquantitative index of myocardial function (24)

The purpose of this study was by non invasive means (STI heart rate arterial blood pressure) to record the changes in cardiac function during pregnancy (the first and third trimester) and the first week of the puerperium together with the response to change in position (supine/left lateral)

MATERIAL AND METHODS

The STI of the left ventricular systole were measured from simultaneous recordings of electrocardiogram (ECG) phonocardiogram (phono) and right carotid arterial pulse tracing (Fig 1) The recordings were obtained on an Elema Mingograph 34® recorder at a paper speed of 50 mm/sec The electrocardiographic lead II was employed A phonomicrophone (EMT 21B amplifier EMT 28B) was placed in the third left intercostal space lateral to the sternum for recording the second heart sound (S_2) The

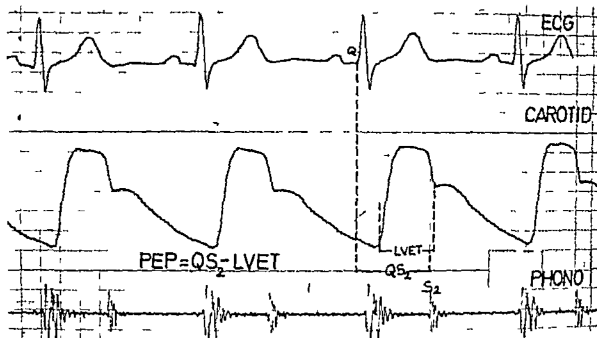


Fig 1 Original tracing showing measurements of QS_2 (total electromechanical systole) *LVET* (left ventricular ejection time) and *PEP* (pre ejection period) from electrocardiogram *(ECG)* carotid pulse curve *(carotid)* and phonocardiogram *(phono)*

carotid pulse curve was recorded with a pressure sensitive pulse receptor (EMT 439A amplifier EMT 29) placed over the right carotid artery

The following STI were measured (see Fig 1) 1) *Total electro mechanical systole* (QS_2) from the onset of the Q wave of the ECG to the initial high frequency vibration of the second heart sound (S_2) 2) *Left ventricular ejection time (LVET)* from the upstroke of the carotid pulse tracing to the dicrotic notch and 3) *Pre ejection period (PEP)* derived by subtracting LVET from QS_2 All intervals were calculated as the mean of ten consecutive beats without tion for HR The ratio between PEP and LVET (PEP/LVET ratio) was calculated from the values of PEP and LVET

Heart rate (HR) was estimated from the R-R interval and arterial blood pressure (BP) was measured by the Riva Rocci method

Thirteen non pregnant women aged 21-32 years (mean 26 years) were used as control group

Thirtyeight women aged 19-4? years (mean ?8 years) in the 8th-12th week of gestation (mean 10 weeks) were studied when admitted for induced abortion (first trimester)

Eleven women aged 2?-39 years (mean 28 years) under going elective Caesarian section were studied the day before surgery (third trimester) and again eight days later (puerperium)

None of the operations were performed on account of maternal disease

The protocol consisted of a 15 minutes stabilization period after which STI HR and BP were obtained in supine and then in left lateral position Three consecutive measurements were obtained in each position with an interval of 5 minutes and then averaged

Table I *STI BP and HR obtained in supine position in non pregnant women during pregnancy and in puerperium (mean values ±S D)*

STI=systolic time intervals QS_2=total electromechanical systole LVET=left ventricular ejection time PEP=pre-ejection period BP=arterial blood pressure HR=heart rate

	QS_2 (msec)	LVET (msec)	PEP (msec)	PEP/LVET (msec/msec)	BP (mmHg)	HR (beats/min)
Non pregnant	416±28	300±26	116±16	0 39±0 07		68±13
1st trimester	392±26	301±20	91±14	0 31±0 05	117/77±10/7	73±12
3rd trimester	356±29	267±18	89±20	0 34±0 08	124/81±15/11	86± 8
Puerperium	380±25	298±17	87±18	0 28±0 06	117/78±14/11	79± 8

Table II *Mean values (±S D) of STI BP and HR measured in the left lateral position during pregnancy and in puerperium*
Abbreviations as Table I

	QS_2 (msec)	LVET (msec)	PEP (msec)	PEP/LVET (msec/msec)	BP (mmHg)	HR (beats/min)
1st trimester	397±74	305±18	92±15	0 31±0 05	101/59±12/10	73±10
3rd trimester	372±23	290±14	82±17	0 29±0 06	118/83±15/13	81± 8
Puerperium	387±31	300±22	85±21	0 29±0 07	113/77±18/12	77± 9

Statistical analysis of the date was based on Wilcoxon tests for paired and unpaired data and Student s *t* test for paired data.

RESULTS

The supine position (Table I)

When compared with the non pregnant (control group) QS_2 and PEP were significantly shorter in the other periods ($p<0\ 01$) PEP/LVET ratio showed a decrease in the first trimester and in the puerperium ($p<0\ 01$) while no difference was observed in the third trimester because of the concomitant shortening of LVET ($p<0\ 01$) HR did only increase in the third trimester ($p<0\ 01$) and in the puerperium ($p<0\ 05$)

Before Caesarian section QS_2 and LVET were shorter ($p<0\ 02$ $p<0\ 01$) and PEP/LVET ratio increased ($p<0\ 02$) when compared to the values obtained eight days later HR was higher before delivery ($p<0\ 02$) while no difference in BP was observed

By comparing the third trimester with the first trimester a shorter QS_2 and LVET ($p<0\ 01$) associated with an increased HR ($p<0\ 01$) was found in the third trimester while no differences in BP were found

The values obtained in the puerperium did not differ from the first trimester values apart from the higher HR ($p<0\ 02$)

The left lateral position (Table II)

In the third trimester a shorter QS_2 and LVET ($p<0\ 01$) and a higher HR and BP ($p<0\ 01$) were found when compared with first trimester

No significant differences were found between the values obtained before and after Caesarian section Nor did the STI in the puerperium differ from the STI in the first trimester besides HR and BP were slightly higher in the former group ($p<0\ 02$ $p<0\ 05$)

The effects of changes in position (Table III)

A significant lengthening in QS_2 and LVET ($p<0\ 01$) and decrease in PEP and PEP/LVFT ratio ($p<0\ 01$ $p<0\ 02$) were observed in the third trimester when the lateral position was assumed Any changes in HR and BP were not significant

In contrast the parameters obtained in the puerperium and first trimester showed no significant differences with change in position apart from a reduction in BP ($p<0\ 01$) in the first trimester

DISCUSSION

The increase in blood volume and cardiac output begins in the late first trimester (10 11 16 22) Blood volume reaches maximum in the third trimester and cardiac output peaks between 24th and

Table III *Significant levels in STI BP and HR by changing position from supine to left lateral*
Abbreviations as Table I

	QS_2	LVET	PEP	PEP/LVET	BP	HR
1st trimester	NS	NS	NS	NS	$p<0\ 01$	NS
3rd trimester	$p<0\ 01$	$p<0\ 01$	$p<0\ 01$	$p<0\ 02$	NS	NS
Puerperium	NS	NS	NS	NS	NS	NS

NS = not significant

32nd week to decline later due to abdominal vascular compression (6 13 21) The rise in cardiac output is brought about by an increased HR and an increased stroke volume (11) Non pregnant levels in blood volume and cardiac output has been reached in the 2nd week of puerperium (16 22)

These hemodynamic changes are in part induced by the increased estrogen and thyroxine production which influence blood volume as well as the strength of myocardial contraction (7 20)

The hemodynamic changes during pregnancy and the first week of puerperium were reflected in all parameters employed in this study

A shorter PEP and a decreased PEP/LVET ratio in the first trimester were found due to the increased blood volume and increased venous return leading to an increased preload The increase in preload results in a shortening of PEP and a decrease in PEP/LVET ratio (24) An increased level of circulating plasma catecholamines due to anxiety and the increase in thyroxine production will further abbreviate PEP (1 8)

Changing to left lateral position in the first trimester does not affect STI or HR but results in a reduction in arterial blood pressure (i e a decrease in afterload) A fall in systolic and diastolic arterial blood pressure in the left lateral position has been described in early pregnancy when recorded by brachial sphygmomanometry (19) and this decrease in afterload induce only minor changes in TI

The compression of the inferior caval vein and e abdominal aorta in the third trimester will lead to a reduction in preload in the supine position and concomitant changes in STI This is further demonstrated when the left lateral position is adopted and the compression thus eliminated the enhanced ventricular filling which follows the changes in position is clearly reflected in the lengthening in LVET abbreviation of PEP and decrease in PEP/LVET ratio (18 24) These signs of improved cardiac performance are also found in the same women 8 days after delivery independent of change of position

However when the values in the first week of puerperium were compared to those of the control group PEP and PEP/LVET ratio were still shorter postpartum which is in agreement with the fact that blood volume in the first week of the puerperium still has not returned to non pregnant levels (16 22) A further evidence for this explanation was demonstrated by comparing the STI from the first trimester with the STI obtained in the puerperium We found no significant differences in any STI between the two groups in either position due to an increased blood volume in both groups

Burg et al (3) have demonstrated a shortening of PEP in the second trimester due to an enhanced myocardial contractility secondary to the increased diastolic filling In the third trimester they found besides a shortening in QS_2 and LVET a lengthening in PEP and PEP/LVET ratio in the supine position because of the impaired venous return while PEP and PEP/LVET ratio in the left lateral position did not differ from predicted values

Rubler et al (17) measured STI on 16 women in supine and sitting positions during pregnancy and six weeks postpartum They found a shorter PEP at the time of maximum expansion of blood volume compared to PEP in the postpartum period which is in agreement with our findings too

In conclusion the non invasively measured STI provide us with more sensitive information about the cardio vascular changes during and after pregnancy than the conventional measurements of heart rate and arterial blood pressure The employment of STI is a useful aid in assessing cardiovascular irregularities in the ante partum and post partum periods The measurement can be repeated frequently without any risk or inconvenience to the patients

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A COMPARATIVE STUDY OF UTERINE ACTIVITY IN LABOUR INDUCED WITH PROSTAGLANDIN F$_{2\alpha}$ OR OXYTOCIN AND IN SPONTANEOUS LABOUR

I *Pattern of the Uterine Contractions*

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Abstract The uterine contraction patterns and the changes in fetal heart rate (FHR) were studied in cardiotocographic recordings from 6 women in oxytocin-induced labour 26 women in PGF$_{2\alpha}$ induced labour and 4 women during the later part of spontaneous labour The contraction patterns and their effect on the FHR did not differ between the three groups During the course of labour an increasing steepness of the upward slope of the contraction wave with increasing intensity of the contraction was found High frequency of atypical contraction patterns suggesting some degree of uterine incoordination was found during the active phase of labour in 10 patients 8 of whom were primiparae This incoordination could not be related to the effect of induction with either drug Incoordinated contractions were associated with longer duration of labour and a tendency to more pronounced acidosis in the infant at birth although mean values still fell in the normal range Ominous FHR patterns were only seen in 2 cases of uterine hyperactivity during induction of labour

Intra-uterine pressure recordings have been used to a great extent for research work and also in routine obstetrics In spite of this fact relatively little attention has been paid to the shape and pattern of the uterine contractions as found on pressure recordings in connection with spontaneous and induced labour It seems to be more or less generally accepted that in normal labour most contractions have a regular form like a Gaussian curve

Baumgarten (3) studied the form of the uterine contractions during normal labour He classified their shapes and categorized them into three different groups based on the relation between the length of the upward and downward slopes of the contraction waves (Fig 2) He observed that with advancing labour higher frequencies of contractions with a steep rise and slow decline were seen and concluded that this type was more effective than other forms in achieving a rapid progress of labour

In the course of his studies of the uterine activity during labour Caldeyro-Barcia (1 9) concluded that atypical patterns in the intra amniotic pressure curve could be the result of incoordinated myometrial activity In this type of labour a new contraction is often superimposed upon the downslope of the preceding one or starts very close to it For this reason the normal decline of the pressure curve to the basal tone level between contractions fails to appear either for longer or shorter periods When incoordination is pronounced it causes slow progress of labour

From clinical trials with prostaglandins used for labour induction a high incidence of incoordinate labour patterns have repeatedly been reported (25 30 34) There are however also reports which state that aberrant labour patterns often occur during spontaneous labour and oxytocin infusions (1 11 13 35 39 40) Few reports seem to have dealt with the question of the incidence of these incoordinations in induced or in spontaneous labour Because the uteroplacental blood flow and hence the fetal well being are highly dependent on uterine function during labour it was thought worth while to compare the pattern of uterine contractility in prostaglandin induced labours with that found in oxytocin-induced or spontaneous labour

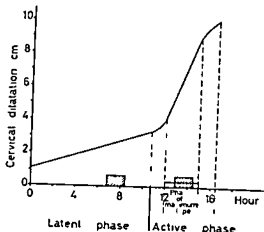


Fig 1 The periods of detailed study of the cardiotocographic recordings indicated (hatched areas) in a partogram After Friedman (14)

MATERIAL AND METHODS

The material comprised 76 women studied during labour In 26 cases labour was induced with prostaglandin $F_{2\alpha}$ (Group P) and in 26 cases with oxytocin (Group 0) Both drugs were given by intravenous infusion at a rate of 3–15 µg/min for $PGF_{2\alpha}$ and of 2–16 mU/min for oxytocin Twenty four women in spontaneous labour served as controls (Group N) They were not given any oxytocic drugs Conduction anesthesia was not used Injections of pethidine and diazepam or inhalations of 50% nitrous oxide/oxygen were used for pain relief Parity and other pertinent clinical data for the patients are given in Table I All the infants were liveborn and healthy and the presentations were normal occiput—anterior vertex Bishop score (5) was always assessed prior to induction

In all cases the intra uterine pressure and the fetal heart e were monitored with cardiotocographic technique diotocographs from Hewlett Packard and Corometrics ere used Open end polyethylene catheters filled with 0 9% saline were used for the pressure recordings In the induction cases the catheters were introduced before the start of the infusion and placed extra amniotically wh h in most cases could be done without rupturing the membranes The validity of intra uterine extra-ovular pressure measurements has been discussed by Csapo (1?) and Hendricks (17) We were able to obtain good recordings in most cases by repeated flushing of the catheter with 0 9% saline In cases of spontaneous labour recordings were started not later than at cervical dilata-tion of 4 cm At this stage the membranes were artifi-cially ruptured in all patients if spontaneous rupture had not already occurred

The fetal heart rate (FHR) was recorded with ultra-sound monitors or by phonocardiography before the membranes were ruptured and thereafter with silver silverchloride electrodes of the clip or spiral type attached directly to the fetal scalp The clinical course of labour was recorded on partograms as proposed by Friedman (14)

In the pressure recordings ‿0 consecutive contractions were studied during each of two different periods of labour The first period corresponds to the late latent phase when regular labour was established and the second to the phase of maximum slope in the partogram curve (Fig 1) We were not able to study the latent phase in the patients with spontaneous labour because most had not come to the delivery ward at this stage of labour In 12 cases of induction of labour (6 from the 0 group and 6 from the P group) it was not possible to obtain satisfactory intrauterine pressure recordings from the early part of the first stage This was due either to technical difficulties with the catheter or the absence of a well defined latent period due to rapid cervical dilatation A pressure recording from the active phase in one multipara in the 0 group had to be discarded for technical reasons

Pressure recordings covering both periods described above were studied and the contractions classified ac-cording to the method described by Baumgarten (Atypical contraction patterns were noted separately atypical were recorded Contractions with a second wa immediately superimposed upon the first one and al pairs of triads of contractions in which the basal ton level was not reached between the contractions becaus the interval between was too short In 16 random

Table I *Pertinent clinical data for the three groups of patients*

	Spontaneous N		Oxytocin O		$PGF_{2\alpha}$ P	
	PP	MP	PP	MP	PP	MP
N	12	12	12	14	12	14
Weeks of pregnancy						
Means	40 9	40 6	41 9	41 3	40 6	39 1
Range	38–42		40–43		36–43	
Pelvic score (means)	–	–	7 0	6 8	4 8	4 5
Birth weight grams (means)	3 657	3 663	3 587	3 756	3 385	3 5 8
Total length of 1st stage hours (means ±1 S D)	11 4±5 1	7 1±3 8	7 2±5 5	3 4±2 2	6 4± 3	4 1±? 1
Total length of 2nd stage minutes (means ±1 S D)	60±39	15±11	43±‿0	11±16	37±31	7±5

		Type I a>b	Type II a b	Type III a<b	Atyp ond I ton
Latent phase	O	3 6	60 2	31 4	4 8
	P	11 6	51 3	27 1	10 0
Active phase	N	3 3	37 8	47 9	11 0
	O	1 0	42 9	49 0	7 1
	P	3 9	42 2	44 2	9 7

Fig 2 Relative frequencies in per cent of the different types of contractions found during the observation periods in the three groups of patients

selected patients 8 from each of the Groups O and P the duration and the amplitude of the contractions was studied more closely The duration was measured to the nearest 0 1 minute at the level of the basal tonus and the intensity to the nearest 5 mmHg.

Values for pH pCO_2 and BD_{ECF} were assessed in blood from the umbilical artery in 35 newborn babies

After the membranes were ruptured the fetal heart rate changes during the rest of the first stage were studied The changes were classified according to the terminology of Hon (19)

RESULTS

he shape of the uterine contraction waves

ı order to get a general idea of the overall distribu on of the different types of contractions in the roups all contractions studied during each part of ibour were pooled for the patients in each group he relative frequencies of the different types of ontractions subsequently found in the three groups f patients are shown in Fig 2 Contractions of type II and III were found in approximately the same roportions in all groups during corresponding ob ervation periods There was however a definite hange from early to late first stage of labour The roportion of contractions of type II to contrac ions of type III was about 2 1 during early labour out changes to about 1 1 in the active phase A change in this direction was observed in 26 of the 39 induction patients studied during both periods Only 5 patients had a lower proportion of type III contractions during the active phase than during the latent phase

Findings from pooled data seemed to indicate that atypical patterns were more common in prostaglandin induced or spontaneous labour than in labour induced by oxytocin However Fig 3 shows that most patients in all three groups had a very low incidence of atypical forms A high proportion of atypical patterns was seen only in the recordings from a small number of patients in each group There was a definite difference in this re spect between primiparae and multiparae Of 10 patients who had more than 5/20 (25%) atypical contractions during the active phase of labour 8 were primiparae Three of the four $PGF_{2\alpha}$ induced patients in this category had atypical patterns during both the latent and active phases of labour Conversely none of the oxytocin inductions showed this type of aberration during both phases Examples of atypical labour patterns from one patient in each group are shown in Fig 4

Relation of the intensity and the duration of the contraction to the shape of the pressure recording

The intensity and duration of contractions of type I II and III were studied in 8 patients from Group 0 and 8 patients from Group P It was found that the duration of the contractions irrespective of type was very constant in the same individuals in both groups of patients with coefficients of varia tion of 7–13% This variation is of the same magni tude as the error of measurement The mean dura tion of the contractions was 1 29±0 15 minutes for the patients from the P group and for the patients in the O group 1 27±0 14 minutes (means ±1 S D) In all the 16 patients the intensity of the type III contractions was higher than for contractions of type II The average ratio in intensity between contractions of type II and type III was 3 4 in both the O and P groups Type I contractions had the lowest intensity but their number was small during the periods studied

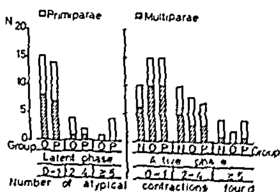


Fig 3 Number of parturients with different degrees of atypical uterine activity in the three groups of patients

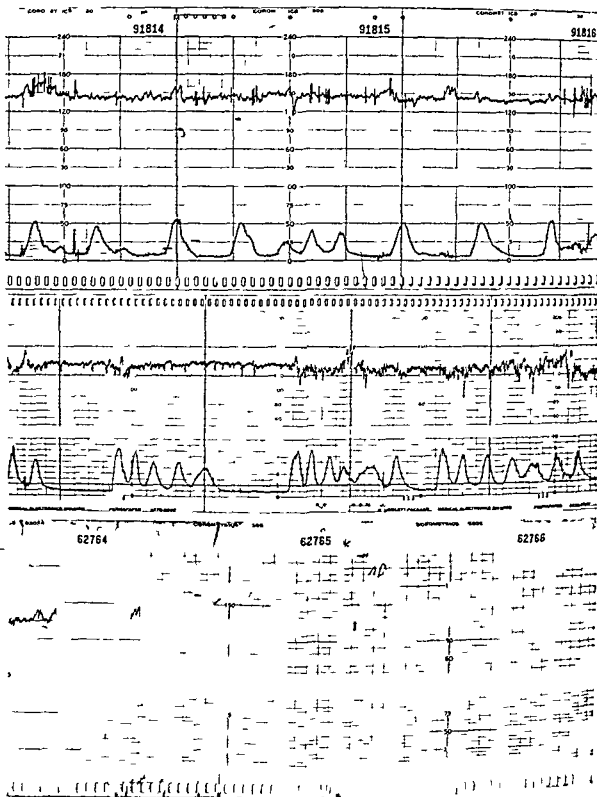


Fig 4 Examples of atypical uterine contraction patterns in 3 patients *Top* Spontaneous labour *Middle* Oxytocin induced labour *Bottom* $PGF_{2\alpha}$ induced labour *Upper recording* Fetal heart rate beats per minute *Lower recording* Intra uterine pressure mmHg

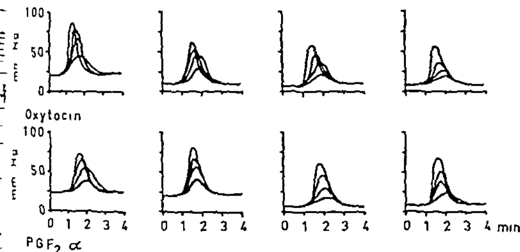


Fig 5 The shape of the uterine contraction at four different dose levels of the induction agent in 4 labours induced with oxytocin (*top*) and $PGF_{2\alpha}$ (*bottom*) Oxytocin 2 4 8 12 mU/min $PGF_{2\alpha}$ 3 6 9 12 µg/min

The constant duration of the contractions and the change of the form of contraction during the course of labour with increasing intensity is also illustrated in Fig 5 Here the contraction patterns in the same patient at four dose levels of the infusion agent are illustrated Details are given in respect of four patients from each of the induction groups It is clearly seen that the upward slope of the intrauterine pressure wave became steeper as the amplitudes of the contraction increased with higher infusion rates of the oxytocic substance

Effects of the shape of the contractions on the progress of labour

The maximum rate of cervical dilatation during the active stage of labour was calculated in all the 36 primiparae and related to the frequency of atypical contraction patterns found for each patient It was found that the maximum rate was 7 3±3 7 cm/hour for primiparae with 0–5% atypical contractions and 3 1±1 9 cm/hour (means and S D) for those with 25% or more The difference was statistically significant ($p<0$ 01) The total duration of the whole first stage in the induction cases was shorter in both primiparae (0 10>p>0 05) and multiparae (0 05>p>0 01) with 5% or less atypical contractions than in those with higher frequencies There was no significant correlation between the proportion of type III contractions during the active phase and the speed of cervical dilatation

Changes in fetal heart rate of the early deceleration type were observed in connection with more than one or two contractions in 17 patients in the whole series No significant differences in the occurrence of early decelerations were found between the groups When early decelerations occurred they were often a rather constant finding in the same patient They were clearly related to the intensity of the contraction Approximately 75% of the early decelerations were found in association with contractions of 45 mmHg or more The form of these contractions was almost exclusively type III FHR-changes were only occasionally observed in connection with atypical contractions even when these occurred frequently (Fig. 4) Late or variable decelerations were seen as short episodes in 2 patients probably caused by maternal hypotension due to compression of the vena cava in the supine position Otherwise late decelerations or prolonged bradycardia (<100 b p m) were observed only in association with high frequency and intensity of contractions and raised basal tonus in one patient in each of the O and P groups

In a previous report on induction with $PGF_{2\alpha}$ (26) we found the *fetal acidosis* at birth to be more pronounced if labour had been incoordinated or included periods of hypertonus Base deficit and pH values in the umbilical artery from 16 cases with less than 5% atypical contractions were therefore compared to the values from 6 cases with 25% or more atypical patterns BD_{ECF} was 5 7±2 8 mEq/l and 8 3±2 5 mEq/l in the two groups and the corresponding pH values 7 28±0 06 and 7 22±0 06 The differences indicated a trend but did not

reach statistically significant levels when tested with Student s *t* test

The *Apgar score* in the 76 infants was 7–10 after 1 minute and 9–10 after 5 minutes

The O and P groups differed with respect to length of pregnancy and pelvic score at the start of the induction of labour We could not find any association between a low pelvic score and the tendency to atypial uterine activity Incoordination was not correlated to the dosage level of the oxytocic agent In the patients with pronounced incoordination this tendency was mostly seen from the start of the infusion even at very low dosage levels

DISCUSSION

When Baumgarten (3) was working on this method of classifying the shapes of contractions he found that contractions with a steep upward slope of the pressure wave (type III) were seen with increasing frequency during the course of labour In late first stage they constituted approximately two thirds of the contractions This is in good agreement with our findings and with those of Tesch et al (36) Baumgarten suggested that this type of contraction is associated with good progress of labour and even that a low percentage might be an indication for stimulation with oxytocin He claimed that oxytocin gives a higher proportion of these effective contractions Our results indicate that the shape of the uterine contractions is related to the intensity spective of the induction agent used This ees with the observation by Thorne et al (38) at the change of pressure with time (dPdT) is closely correlated to the amplitude of the contraction It seems rather probable that a rapid rise in the intra uterine pressure would mean increased efficacy of the uterine activity We could however not demonstrate any direct correlation between the proportion of type III contractions and the maximal speed of cervical dilatation during the active phase

The tendency towards an incoordinated uterine activity during labour differs to a high degree between individuals Quite clearly parity is an important factor It is also true that primiparae are known to show dysfunctional labour more often than multiparae (6 20) As the number of patients with a more pronounced incoordinated activity was rather small in our series it is not possible to form any definite conclusion about differences between the two induction agents in this respect Within the dose range used it can however not be concluded that prostaglandin administration conveys a greater risk of incoordinated labour That the induction agent is not essential for the type of uterine activity found was also suggested by Tchilinguiran (37) after trying both oxytocin and prostaglandins in the same individual

It has been claimed by Jeffcoate (20 39) that uterine incoordination might be caused by a high cervical resistance and this statement is supported by the fact that incoordination is found more often in primiparae In consequence a more close association between incoordination and a short length of pregnancy and a low Bishop score would have been expected This was not the case in this study and a possible explanation is that the series comprises only pregnancies around or at full term

A high frequency of atypical contraction patterns is considered to result in slow progress of labour (1 9 23 32) To a certain degree this was also true in our patients It must be noted however that no patients with really prolonged labours or pronounced uterine inertia were included in the study The progress of labour was in all cases within the normal range as defined by Friedman (15) Lindgren (23 24) has proposed that the slow progress found in incoordinated labour might be mainly caused by the low intensity of many of the contractions in this type of labour This was certainly true for some of our cases It is obvious that a high cervical resistance and uterine incoordination often coexists In those cases it is open to discussion which factor is then the main cause of a slow progress of labour

As has been shown in several experimental studies both in animals and in humans (7 2? ?9) the uterine blood flow during labour is closely related to uterine activity During the contraction the circulation through the placenta is reduced probably mainly due to venous compression and stasis of blood in the intervillous spaces (2) Studies based on temperature changes show that the maximal decrease in the flow is seen during the downslope of the contraction (8) and that an adequate length of the relaxation period is necessary to reach basal flow again after the contraction (31) The normal monophasic contraction in our study had a fairly constant duration during labour which is in agreement with the results of Krapohl et al (?1) The occurrence of prolonged atypical contractions as

defined previously will then result in a prolonged period of impaired circulation through the inter villous spaces If a high frequency of contractions coincides with atypical labour patterns this danger will increase In some cases however atypical complexes seem to be followed by a compensatory pause (Fig 4) and this might give better chances for a return to a normal placental circulation

When the fetal oxygenation is decreased below a critical level during labour the fetus will react with heart rate changes (4 10) As discussed above the uterine contractions have a marked influence on the fetal oxygenation Thus atypical contractions may be expected to provoke FHR changes In fact it has been claimed that decelerations in the fetal heart rate occur with increasing frequency even in connection with a relatively prolonged downslope of the contraction as seen in the type III contraction (11) It has also been reported that with increasing intensity of the uterine activity early FHR decelerations are seen more frequently (35) This is also in good agreement with the findings in various experimental studies (27 28) In our study early decelerations were seen mainly in connection with contractions of rather high intensity but no difference between patients with induced and spontaneous labour was found which is in agreement with several earlier reports (18 40) As FHR decelerations were only occasionally seen together with the atypical contraction patterns in our study it could be concluded that these generally are not the cause of such increased strain to the fetus as might be expected A tendency to a more marked acidosis was however found in the infants of mothers with atypical contractions

The results of the present study do not support the view that oxytocin always gives rise to more regular contraction patterns in comparison to those found in spontaneous labour or following induction with PGF $_{\alpha}$ Oxytocin has sometimes been recommended as a suitable therapeutic agent for the treatment of incoordinate labour (6 23 40) This type of treatment may possibly be successful in some cases but the infusion of an oxytocic agent in the presence of incoordinated labour implies a definite risk that the substance may cause an increase in the frequency of the contractions resulting in inadequate relaxation periods (35) A successive increase of the basal tonus level could also give rise to a tetanic contraction with risk of fetal asphyxia

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RADIOISOTOPE RADICAL OPERATION FOR CANCER OF THE CERVIX[1]

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Abstract By performing the radioisotope radical operation (pre surgical labelling of the lymphatic tissue of the pelvis with colloidal [198]Au) with the aid of a gamma camera it was possible in 78 out of 93 cases to completely extirpate the regional lymphatic tissue of the pelvis In eight out of 24 cases with positive findings on the lymph nodes we were also able to extirpate with this technique residues of carcinomatous lymphatic tissue during the course of a secondary isotope lymphadenectomy This fact is likely to further improve the recovery rate—all the more so since even the scanner and eye probe technique already reduced the mortality rate due to recurrence by 16 4% after 5 years

Ever since the introduction of mandatory lymphadenectomy in abdominal radical operations for cervical carcinoma it has been generally assumed that a complete extirpation of the regional lymphatic tissue is not possible Efforts to label regional lymph nodes with lipiodol (1 2 3 13 14) and dyes (12 15) were only of partial success This method did not allow to detect and extirpate nodes which were concealed by blood vessels and ligaments In order to tackle this drawback the radioisotope operation for cancer of the cervix uteri has been developed The surgical procedure consists in pre operative radioactive colloidal gold labelling of the lymphatic tissue in the pelvic region

MATERIALS AND METHODS

To this end 100 μCi colloidal Au per extremity are administered subcutaneously between the first and second toes 4 hours before the operation During surgery labelled lymphatic tissue may be scanned and extirpated thus significantly enhancing the radical nature of the lymphadenectomy in conventional surgery this lymphatic tissue due to lack of visibility cannot be removed

The radioisotope radical operation has undergone three phases of development in the first one a Magna Picker Scanner 3 was used in order to pinpoint radioactively labelled tissues not removed as yet in phase 2 the technique was improved by introducing an eye probe (4 5 6 7) Success was underlined by fact that in 4 out of 10 cases of carcinomatous lymph nodes extirpation of tumour tissue residues was possible in the course of a secondary specific intervention At this particular site a recurrence might be avoided The mortality rate due to recurrence was thus lowered to 16 4% five years postoperatively (Table I) this is an improvement compared to the results of the conventional Wertheim radical operation Nevertheless the figures did not quite conform to our expectations since in only 57 6% of all cases operated during the years 1969 1970 and 1971 was it possible to extirpate completely the labelled lymphatic tissue

For the above mentioned reason we decided to try and develop phase 3 of the radioisotope radical operation—introducing a surgical gamma camera that we had designed ourselves (Fig 1) Since the beginning of 1972 this camera has been in use at our clinic (Fig 2) (8 9)

The fundamental difference between the scanner and eye probe methods on the one hand and the camera technique on the other hand may be described as follows with the scanner and eye probe the radioactively labelled tissue

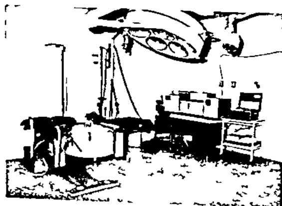


Fig 1 The surgical gamma camera unit

[1] Presented in part at the Thirteenth Congress of the Pan Pacific Surgical Association Honolulu Hawaii Feb 15–21 1975

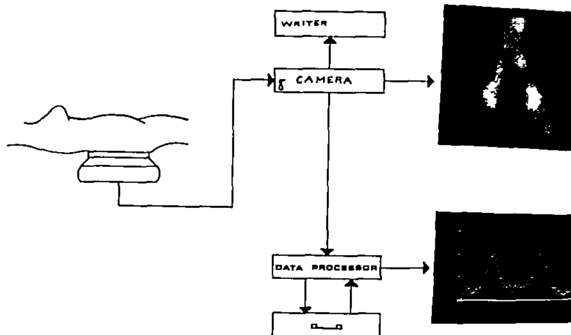


Fig 2 Scheme of the surgical gamma camera unit with oscilloscope and profile pictures

has to be scanned with a 3 in crystal across a large area whereas the use of the camera permits the entire field of surgery to be included in the crystal field of the detector head—thus making possible an overall image of the radioactively labelled tissue on the camera s oscillator screen During this procedure the patient does not lie on a conventional operating table but on a specially adapted collimator surface of the gamma camera (Fig 2) The entire pelvis is positioned on the crystal disc (30 cm in meter) of the camera s detector head Since the top er the operating table is positioned on the left side o collimator disc (when viewed from the tripod) the th and arm supports are attached on the same side administering anesthesia To the right of the tripod

Table I *Recurrences in conventional and radio-isotope radical operations*

Period of	No of cases	Death by recurrence	Mortality could be reduced by
Group I			
Wertheim surgery			
1965	61	9	
1966	44	5	
1967	49	9	
Total	154	23=14 93% ~15%	16 38% ~16 4%
Group II			
Radio isotope radical operation with colloidal ^{198}Au Nov 1969 until March 31 1971	40	5=12 5%	

In Group I 65 1% of cases were found at stage I
In Group II 67 5% of cases were found at stage I

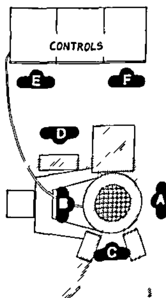


Fig 3 Scheme of the surgical gamma camera unit during the operation *A*=surgeon *B*=first *C*=second assistant *D*=anesthesist *E* and *F*

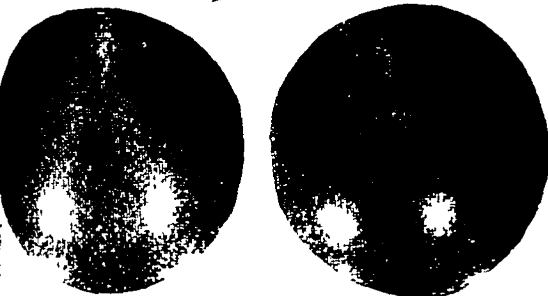


Fig 4 Oscilloscope picture before primary lymphadenectomy (left) and after surgery (right)

supports are attached in a way resembling a Wertheim operating table—with the second assistant standing between the legs of the patient The surgeon works at the side of the detector head where there are not other attachments the first assistant facing him i e he stands between the U shaped struts of the support (Fig 3)

24 hours after labelling with radioactive gold the radical operation according to Latzko–Wertheim–Meigs is performed lymphadenectomy being carried out before removal of the surrounding tissue Following the classical extirpation of the internal genitals including the surrounding paratissue and primary mandatory lymphadenectomy the residual lymphatic tissue is visualized on the oscillator (Fig. 4)

The secondary isotope lymphadenectomy is performed by a second and well rested surgical team since such an operation requires utmost concentration The preoperative lymphscan is made to coincide with a coordinate grid conforming to the oscillator screen of the camera Certain squares on this screen are assigned to the lymphatic tissue areas of the scintigram We call them areas of interest with activities to be visualized as profiles they may be counted with the camera s digital unit and recorded with a polaroid camera There is three-dimensional recording—a top view on the oscillator screen a profile view in the 3rd dimension and a depth view If there is no chance to extirpate all affected lymphatic tissue with this grid technique there is still the possibility of locating residual labelled tissue with a cobalt rod (^{57}Co) (Fig 5) The luminous spot produced by this cobalt rod on the screen of the oscillator is sited to coincide with the residual lymphatic tissue at this point the specific area has to be vertical to the cobalt rod in either a dorsal or a ventral direction Thus we are always able to locate and extirpate tissue even if it is concealed by major vessels or ligaments

This surgical intervention is completed once the profile of activity recorded over the respective lymphatic tissue area does not exceed basic pulse values (Fig 6) Subsequently quadruple abdominal drainage is performed one redon drain being inserted on either side into pararectal fossa and the obturator fossa Then peritoneum and abdominal wall are closed Postoperative treatment is performed according to the Vienna method (10 11)

RESULTS

Up to now 93 subjects have been operated on with the aid of the gamma camera with radioactive colloidal gold labelling prior to surgery Complete ex



Fig 5 Cobalt rod (^{57}Co) which is used for detection of radioactivity

Fig 6 Oscilloscope and profile pictures before secondary lymphadenectomy showing residual lymphatic tissue (left) and after secondary isotope lymphadenectomy showing that the pelvis is cleaned up (right)

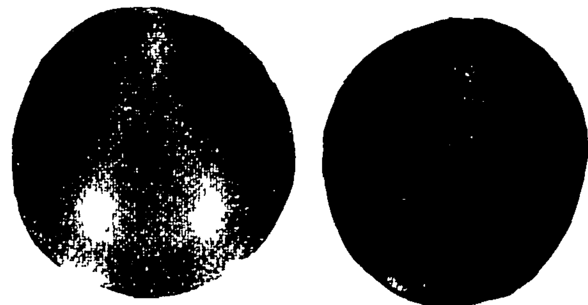


Fig 7 Oscilloscope picture before radioisotope radical operation showing ^{198}Au labelled lymphatic tissue (left) No labelled lymphatic tissue can be visualized after surgery except for the upper part of the inguinal lymp nodes (right)

able II *Gammacamera method and capacity of mphadenectomy*

	Lymphadenectomy	
No. of cases	Complete	Not complete
93 100%	78=83 8%	15=16 2%

irpation of the labelled tissue was possible in 78 patients (83 8%) (Fig 7 and Table II) This improved technique of lymphadenectomy proved to be particularly valuable in cases with gland involvement In eight out of 24 cases with histologically verified positive lymph nodes additionally affected could be extirpated within the scope of a ry specific lymphadenectomy All groups l lymph nodes in all 93 patients and even those carcinoma invasion could be detected No oactive gold is taken up by those lymph nodes which are completely invaded by the carcinoma But in such cases the nodes are already enlarged and palpable and therefore often surgery is impossible in these subjects There was no such a case among our patients This fact is likely to result in further improvement of the statistics since—as mentioned above—a 16 4% reduction of the recurrence mortality rate had already been recorded for stages I and II over a five year period

COMMENTS

Statistics demonstrating the absence of mortality and the unchanging morbidity level (ileus 0 mortality 0 thrombosis 0 peritonitis 0 ureter fistula frequency 1 07% no other fistulae) encouraged us to report our technique in radioisotope radical operations

Because of the expected improvement of the recovery rates subsequent to surgical treatment of cervical carcinoma we would like to submit this method for scrutiny

In all cases mentioned above radioactively labelled tissue could be removed during the secondary radioisotope lymphadenectomy and in some 30% of lymph node positive cases additional cancerous lymph glands were found This clearly shows that the usual lymphadenectomy which has been known for a long time to be not radical enough can be considerably improved by this method

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SHORT COMMUNICATION

SERUM LEVELS OF THE PREGNANCY ZONE PROTEIN DURING THE NORMAL MENSTRUAL CYCLE

Mats Goran Damber [1] Bo von Schoultz [1] Torgny Stigbrand[2] and Kjell Carlstrom[3]

From the [1]Departments of Obstetrics and Gynecology (Head Prof P Lundstrom) and [2]Physiological Chemistry (Head Prof K -G Paul) University of Umea Umeå Sweden and the [3]Department of Obstetrics and Gynecology (Head Prof A Ingelman Sundberg) Sabbatsberg Hospital Karolinska Institutet Stockholm Sweden

he induction of the immunosuppressive serum otein PZ (pregnancy zone protein) caused by estrogens is well known Increased levels of PZ e found during pregnancy during treatment with al contraceptives and conjugated oestrogens and males treated with oestrogens for prostatic can er (1–4) The recent development of a sensitive dioimmunoassay for this protein has made it ossible to measure the low basic levels and age ependent increase in serum PZ concentration resent in males and in non pregnant healthy males (5 6) Due to the oestrogen dependent in uction of PZ synthesis it could be expected that the variation in endogenous oestrogen levels during the menstrual cycle would influence the PZ levels The present communication describes simultaneous measurement of PZ low polar oestrogens progesterone LH and FSH during normal menstrual cycles

EXPERIMENTAL

Serum samples were obtained from 12 apparently healthy women of various ages during their menstrual cycle Five of these women were followed with daily samples The sera were stored at −20°C until analysis Each sample was coded and tested blindly in duplicate Serum levels

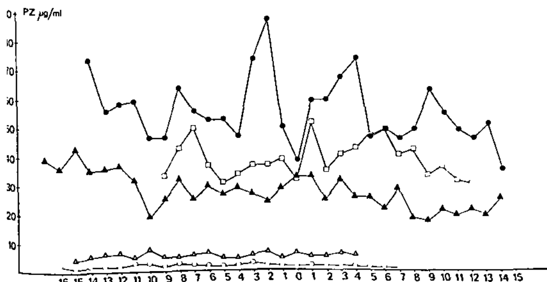


Fig 1 Serum levels of PZ in five complete menstrual cycles Ovulation is indicated by day 0

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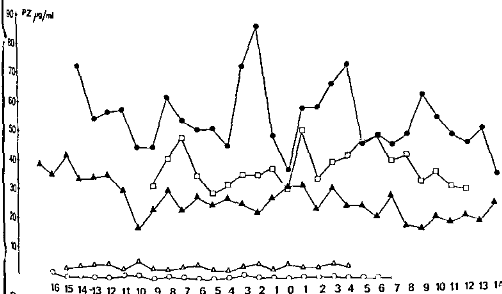


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of PZ FSH LH low polar oestrogens (LPE i e im munoreactive oestrogens) and progesterone were de termined by radioimmunoassay techniques as previously described (5–11)

RESULTS AND COMMENTS

The levels of PZ during five complete individual cycles are shown in Fig 1 No significant pattern in the PZ levels could be found and there was no statistically significant correlation between the levels of PZ and of any of the hormones The PZ values ranged between 2–80 μg/ml and as has been shown previously the higher values were present in the older women (6) There was a pronounced intra individual variation in the PZ levels The results indicate that the peak values of oestrogens during the normal menstrual cycle are not of sufficient magnitude or duration to induce increased serum levels of PZ There are still no basic data available concerning lag time and threshold levels for the oestrogen induced synthesis of PZ

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11 Antibody against progesterone 11α hemisuccinate BSA raised in sheep (Royal Veterinary College Stockholm Sweden) Dextran coated charcoal separation

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Letter to the Editor

Dear Sir!

We have studied with great interest a recent article published in Acta Obstet Gynecol Scand by Drs Maltau and Andersen Continuous epidural anesthesia with a low frequency of instrumental deliveries (Acta Obstet Gynecol Scand *54* 401 1975) As their results and conclusions are somewhat different from ours (1) we would like to make the following comments

The authors main point is that epidural analgesia in labour will not increase the frequency of instrumental deliveries In the introduction they refer to two studies (3 6) in which the same conclusions were made It should therefore be noted that the frequency of instrumental deliveries in the actual studies were Doughty 42% for primipara and 11% for multipara while Potter reported 25–30% instrumental deliveries in primiparae In comparison with Maltau & Andersen s as well as with our own (1) control group without epidural block these figures are still relatively high

We do anyhow also think that the frequency of instrumental deliveries after epidural block can be kept at an almost normal figure This will however lead to an increased duration of the second stage of labour Crawford a leading authority with in this field as well as Potter which were referred to in Maltau & Andersen s study have noted this increased duration of the second stage of labour (2 6) Crawford also does advocate an increased frequency of instrumental deliveries to counteract this phenomenon

The second stage of labour imposes an increased stress on the fetus and should not be delayed Acid–base studies (4 8) have clearly demonstrated this

We think that the neonate is better off after an instrumental delivery and a normal second stage than after a prolonged second stage and a spontaneous delivery When using epidural block in labour a normal frequency of instrumental deliveries is not in the best interest of the newborn

Maltau & Andersen state in their discussion that the second stage never exceeded 1 hour This figure seems questionable when for example Crawfords figures regarding the duration of the second stage after epidural block in about 1000 patients are studied (2) In our own experience a frequency of instrumental deliveries of at least 40% in primiparae is needed to keep the second stage to approximately 1 hour Did Maltau & Andersen use fundal pressure and episiotomy in all patients?

The figures reported by Maltau & Andersen regarding the doses per hour of Bupivacaine are rather unusual Bupivacaine was injected approximately every hour (every 45 min in multiparae) which is probably the shortest dose interval published for 0 25% Bupivacaine (with or without adrenaline) Previous studies (1 2 7) have demonstrated a dose interval of aproximately 2 hours which is one of the main advantages of Bupivacaine while dose intervals of approximately 1 hour are mainly seen with shorter acting agents like lidocaine (8)

Finally it was noted that in 19 cases the indication to epidural block was intrauterine distress This is a rather uncommon indication and it would be interesting to know how the diagnoses were made (continuous fetal heart rate monitoring or fetal scalp blood sampling) and in which way these parameters changed after the initiation of an epidural block

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INDEX

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